Stimulants and Related Agents

Therapeutic Class Review (TCR)

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FDA-APPROVED INDICATIONS

Drug	Manufacturer	ADHD			Narcolepsy (age ≥6 years)	Other Indications
		age 3-5 years	age >6 years	Adults		
Stimulants: Immediate-Release						
armodafinil (Nuvigil®)[1]	Cephalon					Excessive sleepiness associated with narcolepsy, OSA/HS* and SWSD for age ≥17 years
dexmethylphenidate IR (Focalin™)[2]	generic, Novartis		X			
dextroamphetamine IR (Zenzedi™)[3]	generic, Arbor	X	X		X	
dextroamphetamine solution (Procentra™)[4]	generic,	X	X		X	
methamphetamine (Desoxyn®)[5]	generic		X			Exogenous obesity in adults
methylphenidate IR (Methylin®, Ritalin®)[6,7]	generic, Shionogi		X			
mixed amphetamine salts IR (Adderall®)[8]	generic		X		X	
modafinil (Provigil®)[9]	generic, Cephalon					Excessive sleepiness associated with narcolepsy, OSA/HS* and SWSD for age ≥16 years
Stimulants: Extended-Release						
dexmethylphenidate ER (Focalin XR™)[10]	generic (15 mg, 30 mg, 40 mg), Novartis		X	X		
dextroamphetamine ER (Dexedrine®)[11]	generic		X		X	
lisdexamfetamine dimesylate (Vyvanse™)[12]	Shire		X	X		
methylphenidate SR (Ritalin SR®*, Metadate ER®)[13,14]	generic		X		X	
methylphenidate ER OROS (Concerta®)[15]	generic, OMJPI		X	X		
methylphenidate ER (Metadate CD®)[16]	generic, UCB		X			
methylphenidate ER (Quillivant™ XR)[17]	NextWave		X			
methylphenidate ER (Ritalin LA®)[18]	generic, Novartis		X			

FDA-Approved Indications (continued)

Drug	Manufacturer	ADHD			Narcolepsy (age ≥6 years)	Other Indications
		age 3-5 years	age >6 years	Adults		
Stimulants: Extended-Release *(continued)*						
methylphenidate transdermal (Daytrana™)[19]	Noven		X			
mixed amphetamine salts ER (Adderall XR®)[20]	generic, Shire		X	X		
Non-Stimulants						
atomoxetine (Strattera®)[21]	Eli Lilly		X	X		
clonidine ER (Kapvay™)[22]	generic, Shionogi		X			Treatment of ADHD as adjunct to stimulants
guanfacine ER (Intuniv™)[23]	Shire		X			Treatment of ADHD as adjunct to stimulants

OSA/HS – obstructive sleep apnea/hypopnea syndrome SWSD – shift work sleep disorder.

* In OSA/HS, modafinil and armodafinil are indicated as an adjunct to standard treatment(s) (e.g., continuous positive airway pressure [CPAP]) for the underlying obstruction.

OVERVIEW

Attention-deficit/Hyperactivity Disorder (ADHD)

The most common use of stimulants is for the treatment of Attention Deficit/Hyperactivity Disorder (ADHD), for which they are considered first-line therapy.[24,25,26,27,28,29] ADHD, which affects four to 12 percent of school-age children and about four percent of adults, is a chronic condition with core symptoms of inattention, hyperactivity, and impulsivity.[30,31,32] It may also be accompanied by internalized disorders such as sadness and anxiety, as well as aggressive and oppositional disorders.[33,34,35] The three main types of ADHD are primary hyperactive, primary inattentive, and mixed.

Children with ADHD may experience academic underachievement, difficulties in personal relationships, and low self-esteem.[36,37] Early recognition of the signs and symptoms of ADHD, assessment, and treatment can help redirect the educational and social development of most children with ADHD. According to the 2011 ADHD guidelines formulated by a Subcommittee of the American Academy of Pediatrics (AAP), the primary care clinician should initiate an evaluation for ADHD for any child four through 18 years of age who presents with academic or behavioral problems and symptoms of inattention, hyperactivity, or impulsivity.[38] The treatment of patients with ADHD should maximize function to improve relationships and performance at school, decrease disruptive behaviors, promote safety, increase independence, and improve self-esteem.

According to the 2011 ADHD guidelines in children and adolescents, the AAP recommends parent- and/or teacher-administered behavior therapy as first line treatment for children four to five years of age.[39] Methylphenidate may be prescribed if the behavior interventions do not provide significant improvement and there is moderate-to-severe continuing disturbance in the child's function. For children six to 11 years of age, the evidence is particularly strong for use of stimulant medications and

sufficient, but less strong, for atomoxetine, extended-release guanfacine, and extended-release clonidine; medication therapy in addition to behavioral therapy is recommended. For patients 12 to 18 years of age, AAP recommends FDA-approved medications with the assent of the adolescent and behavior therapy as treatment for ADHD, preferably both.

Although symptoms of ADHD tend to improve with age, this may be due in part to improved coping skills. The continuation of synaptogenesis and myelinization into adolescence and young adulthood (especially in the frontal lobes) may also play a role in the improvement of symptoms with age. Sixty to 80 percent of children with ADHD will still require treatment through adolescence and into adulthood.[40,41,42,43]

Studies have shown that 70 to 75 percent of patients respond to the first stimulant medication on which they are started.[44] Response increases to 90 to 95 percent when a second stimulant is tried. Treatment failures with stimulants are often due to improper doses rather than ineffectiveness of the medication. It may take one to three months to adequately establish the best dose and form of medication for any given patient. The AAP recommends that, if a trial with one drug compound group is ineffective or poorly tolerated, a trial on a medication from another group should be tried.[45]

Treatment of ADHD in preschool children typically begins with a parent-training intervention. The Medical Letter suggests for school-age children, to begin with an oral stimulant, noting that none of these agents has been shown to be more effective than another.[46] They indicate that short-acting stimulants may be useful in small children to demonstrate effectiveness or in instances where there is not an appropriately low dose of a long-acting agent. The methylphenidate patch (Daytrana) is recommended for use when oral administration is problematic. Atomoxetine (Strattera), a non-stimulant agent, is recommended if there are objections to using a controlled substance, if stimulant-induced weight loss is problematic, or for patients with anxiety, mood, tic, or substance abuse disorders. Extended-release formulations of guanfacine or clonidine may be helpful when used concurrently with a stimulant in patients who cannot tolerate usual doses of the stimulant, particularly those with tics. Mixing short- and long-acting stimulants can be helpful to achieve an early stimulant effect for early-morning school classes or for reducing rebound irritability or overactivity toward the end of the day, especially when studying in the evening.

Hypersomnolence

Excessive sleepiness, or hypersomnolence, is the primary and often debilitating symptom experienced by patients with narcolepsy, obstructive sleep apnea/hypopnea (OSA/HS), and shift work sleep disorder (SWSD). The defining characteristic of hypersomnolence is a consistent inability to stay awake and alert enough to safely and successfully accomplish tasks of daily living. Persons experiencing excessive sleepiness who seek medical attention typically complain of fatigue, tiredness, lapses of attention, lack of energy, low motivation, difficulty concentrating, disrupted sleep, snoring, or difficulties at work.

While continuous positive airway pressure (CPAP) has been shown to improve daytime sleepiness in patients with OSA, the level of sleepiness does not always normalize.[47,48,49,50,51,52] To address this residual daytime sleepiness, pharmacologic treatments may be beneficial in users of CPAP. While CNS stimulants such as dextroamphetamine (Dexedrine, Procentra), methylphenidate (Methylin, Ritalin, Ritalin SR, Metadate ER, Metadate CD, Ritalin LA, Quillivant XR), and mixed amphetamine salts (Adderall, Adderall XR) have been used for this purpose, the potential for adverse cardiovascular

events may be of concern, especially in this overall high-risk patient population.[53] Due to their lack of sympathomimetic activity, modafinil (Provigil) and armodafanil (Nuvigil) are relatively free of adverse cardiovascular effects and may be preferable to the stimulants for the treatment of excessive daytime sleepiness resulting from OSA.[54,55]

Obesity

Other CNS actions or metabolic effects may be involved, in addition to the appetite suppression caused by stimulants.[56] In relatively short-term clinical trials, adult subjects instructed in dietary management and treated with stimulants lost more weight on average than those treated with placebo and diet. However, the magnitude of increased weight loss of drug-treated patients over placebo-treated patients is only a fraction of a pound per week. The rate of weight loss is greatest in the first weeks of therapy for both drug and placebo subjects and tends to decrease in subsequent weeks. Methamphetamine (Desoxyn) is FDA-approved in adults for short-term adjunctive therapy in a weight reduction regimen based on caloric restriction for patients in whom obesity is refractory to alternative therapy.

PHARMACOLOGY

Stimulants act by blocking the reuptake of norepinephrine and dopamine into the presynaptic neuron and increasing their release into the extraneuronal space. Amphetamines appear to release newly synthesized dopamine while MPH causes the release of stored dopamine.[57] Unlike MPH, the amphetamine-induced elevation of synaptic dopamine does not appear to be highly dependent upon impulse-released dopamine. Stimulants tend to have selectivity for cortical, rather than striatal, dopamine presynaptic terminals. As a result, lower doses have more of an effect on attention than on motor activity.

Symptoms of inattention in ADHD may be due to dopamine and/or norepinephrine dysfunction in critical areas of the cerebral cortex controlling cognition. It seems as though patients with such symptoms need a boost in their dopamine/norepinephrine and, when they are given agents such as stimulants that boost these systems, their symptoms of inattentiveness can improve.

Symptoms of hyperactivity and impulsivity associated with ADHD are more likely mediated by the nigrostriatal dopamine pathway, which controls motor activity. Due to a presumed greater sensitivity of the mesocortical dopamine terminals in patients with ADHD, lower doses of stimulants prefer the cerebral cortex. Thus, the effects of stimulants on inattentiveness usually appear before their effects on motor behaviors.

Amphetamine and MPH are available as racemic or single isomer products. The d-enantiomer of amphetamine, dextroamphetamine (Dexedrine, Zenzedi, Procentra), has much less of an effect on norepinephrine release than the l-enantiomer. Thus, the combination of the two isomers of amphetamine may provide additional benefit over dextroamphetamine in some patients. This combination is available as mixed amphetamine salts (Adderall, Adderall XR), which contains d- and l-amphetamine in a 3:1 ratio. Mixed amphetamine salts tends to have fewer adrenergic side effects than MPH. MPH is a racemic mixture of d- and l-enantiomers, the former of which is more pharmacologically active.[58,59] A product containing only the d-enantiomer, dexmethylphenidate (Focalin, Focalin XR), is available. Lisdexamfetamine dimesylate (Vyvanse) is a prodrug in which d-amphetamine is covalently bonded to L-lysine and converted to these components by enzymatic hydrolysis.[60] Lisdexamfetamine is rapidly absorbed from the gastrointestinal tract after oral

administration and converted to dextroamphetamine, which is responsible for its activity. Conversion is believed to occur by first-pass intestinal and/or hepatic metabolism. Metabolism does not occur by cytochrome P450 enzymes.[61]

Compared to immediate-release dosage forms, extended-release preparations offer the advantages of less fluctuation in activity and removal of the need for dose administration in school. Their prolonged action, however, may be less intense, and their use forfeits the advantages of flexibility and control of titrating that the more frequent dosing schedule of immediate-release dosage forms.[62] It is also important that extended-release dosage forms do not produce a flat plasma concentration of the stimulant, which could lead to acute tolerance.[63] There is increased experience with combining immediate- and extended-release preparations to produce optimal symptom control throughout the day.

Atomoxetine (Strattera) is a selective inhibitor of the presynaptic norepinephrine transporter. It increases norepinephrine and dopamine levels, especially in the prefrontal cortex.[64] It has minimal affinity for other monoamine transporters. Its mechanism of action suggests that atomoxetine is unlikely to have abuse potential or to cause motor tics.[65,66] Atomoxetine has a slower onset of action than do stimulants; therapeutic effects may not be seen until a week after the start of treatment. Atomoxetine has a longer duration of action than the stimulants with the possibility of symptom relief during the evening and early-morning hours.[67]

Guanfacine ER (Intuniv) is a selective alpha-2A-adrenergic receptor agonist.[68] Clonidine (Kapvay) is a centrally acting alpha-2-adrenergic receptor agonist.[69] These drugs reduce sympathetic nerve impulses to the heart and blood vessels leading to a decrease in blood pressure. This mechanism of action in the treatment of ADHD is not known.

Modafinil (Provigil) appears to act by selective activation of the cortex without generalized stimulation of the CNS. It has wake-promoting actions like the sympathomimetic agents. It also causes psychoactive and euphoric effects, as well as the alterations in mood, perception, thinking and feelings typical of other CNS stimulants. *In vitro*, modafinil binds to the dopamine reuptake site and causes an increase in extracellular dopamine. In vivo models, however, have not detected enhanced dopaminergic activity. Modafinil, then, may also work through other neurotransmitter systems. Armodafanil (Nuvigil) is the R-enantiomer of modafinil. Both armodafinil and modafinil have shown similar pharmacological properties.

PHARMACOKINETICS

Drug	Time(s) to Peak Concentration(s) (hours)	Onset of Action (minutes)	Half-Life (mean, in hours)	Duration of Action (hours)	Extended-Release Delivery System (where applicable)
Stimulants: Immediate-Release					
armodafinil (Nuvigil)[70]	2	--	15	--	--
dexmethylphenidate (Focalin)[71]	1-1.5	30	2.2	4-6	--
dextroamphetamine IR (Zenzedi)[72,73]	2-3	20-60	children: 6-8 adults: 10-12	4-6	--
dextroamphetamine solution (Procentra)[74]	--	--	11.75	--	--
methamphetamine (Desoxyn)[75]	--	--	4-5	--	--
methylphenidate IR (Methylin, Ritalin)[76,77]	1.5-3	15-20	2-4	2-4	--
mixed amphetamine salts IR (Adderall)[78]	3	30-60	children: 9-11 adults: 10-13	4-8	--
modafinil (Provigil)[79]	2-4	--	15	--	--
Stimulants: Extended-Release					
dexmethylphenidate (Focalin XR)[80]	1.5, then 6.5	--	children: 2-3 adults: 2-4.5	Children: 8-12 Adults: 8	50% each IR and enteric-coated, delayed-release beads
dextroamphetamine ER (Dexedrine)[81]	8-10	60-90	children: 6-8 adults: 10-12	6-10	initial dose delivered immediately with remaining medication released over 6-8 hours
lisdexamfetamine dimesylate (Vyvanse)[82,83,84]	dexamfetamine = 3.5* (prodrug = 1)	--	10-13 (prodrug <1)	~ 10	Active drug slowly released by rate-limited hydrolysis
methylphenidate SR (Metadate ER)[85,86,87]	1.5-4.7	30-180	2-4	3-8	various
methylphenidate ER OROS (Concerta)[88,89]	1-2, then 6-8	30-60	3.5	8-12	22% IR overcoat; 78% controlled release core; osmotic-release oral system
methylphenidate ER (Metadate CD)[90]	1-1.5, then 4-4.5	30-90	6.8	7-12	30% IR, 70% ER beads
methylphenidate ER (Quillivant XR)[91]	5	45	5-5.2	12	extended-release oral suspension

Pharmacokinetics (continued)

Drug	Time(s) to Peak Concentration(s) (hours)	Onset of Action (minutes)	Half-Life (mean, in hours)	Duration of Action (hours)	Extended-Release Delivery System (where applicable)
Stimulants: Extended-Release *(continued)*					
methylphenidate ER (Ritalin LA)[92]	1-3, then 4-8	30-110	2.5-3.5	7-12	50% dose IR beads, 50% dose enteric–coated, delayed release beads
methylphenidate transdermal (Daytrana)[93]	7.5-10.5	120	3-4	~ 3 hours after patch removal	concentrated drug cells in patch
mixed amphetamine salts ER (Adderall XR)[94]	7**	30-60	children: 9-11 adults: 10-13	8-10	50% each of immediate- and delayed-release beads
Non-Stimulants					
atomoxetine (Strattera)[95]	1-2	3-4 weeks	5.2	~24	--
clonidine ER (Kapvay)[96]	6.5-6.8	--	12-16	--	extended-release tablet
guanfacine ER (Intuniv)[97]	5-6	--	18 (adults)	--	matrix consisting of ionic polymers, enteric polymers, and organic acids

* Food prolongs the Tmax of converted prodrug (d-amphetamine) by one hour

** Food prolongs the Tmax of mixed amphetamine salts ER by 2.5 hours

The half-life and blood concentration of amphetamine is directly related to urinary pH, increasing with alkaline pH and decreasing with acidic pH. For every unit increase in pH, the half-life of mixed amphetamine salts (Adderall, Adderall XR, Procentra) increases by an average of seven hours. As a result, urine acidifying agents (e.g., ammonium chloride, sodium acid phosphate) and urine alkalinizing agents (e.g., acetazolamide, some thiazides) should be avoided, if possible, to maintain consistent amounts of the active drug in the system.

Except for mixed amphetamine salts, stimulants are de-esterified in the liver to pharmacologically inactive metabolites. In contrast, mixed amphetamine salts are metabolized in the liver by hydroxylation, dealkylation, and deamination. Urinary excretion accounts for nearly all of the elimination of the stimulants and atomoxetine (Strattera), as well as their metabolites.

Methylphenidate extended-release OROS (Concerta) and dexmethylphenidate ER (Focalin XR) have similar pharmacodynamic profiles, with the main difference being that the latter contains only dexmethylphenidate. The release profiles of Metadate CD and Ritalin LA, also extended-release formulations of MPH, are very similar to each other.

When opened and sprinkled on cold applesauce, the bioavailability of methylphenidate ER (Metadate CD and Ritalin LA), dexmethylphenidate ER (Focalin XR), and mixed amphetamine salts ER (Adderall XR) are the same as the intact capsules. Dextroamphetamine SR (Dexedrine) capsules can also be opened and sprinkled on food. Lisdexamfetamine (Vyvanse) capsules may be opened and the entire contents

dissolved in water and consumed immediately. Atomoxetine capsules are not to be opened as they are an ocular irritant. Quillivant XR is an extended-release suspension that is reconstituted with water and shaken for at least 10 seconds.

Atomoxetine is metabolized in most patients primarily by the CYP2D6 enzymatic pathway. Medications that inhibit CYP2D6 (e.g., paroxetine, fluoxetine, and quinidine) increase the bioavailability of atomoxetine. Atomoxetine does not appear to induce or inhibit the CYP2D6 enzyme system.[98] Approximately five to 10 percent of patients are "slow metabolizers" in which the mean half-life of atomoxetine is 21.6 hours, over four times longer than in "rapid metabolizers."[99]

Atomoxetine has a slower onset of action than the stimulants; onset of effect may take one week and full effect may not be seen for up to four weeks.[100,101] The effects of atomoxetine appear to last longer than would be expected from its pharmacokinetic profile.[102] The reasons for these pharmacokinetic – pharmacodynamic differences are not clear, but may be due to a variance between brain and plasma pharmacokinetics, or by continued effects on the norepinephrine transporter.

Exposure to guanfacine ER (Intuniv) was higher in children (ages six to 12 years) compared to adolescents (ages 13 to 17 years) and adults, probably attributable to the lower body weight of children compared to adolescents and adults.[103] The pharmacokinetics of a single dose of guanfacine ER 4 mg was affected when administered with a high-fat breakfast. The mean exposure increased (Cmax 75 percent and area under the curve [AUC] 40 percent) compared to dosing in a fasted state.

CONTRAINDICATIONS/WARNINGS[104,105,106,107,108,109,110,111,112,113,114,115,116,117,118,119]

Contraindications

All products in this review, except clonidine ER (Kapvay) and guanfacine ER (Intuniv), are contraindicated during or within 14 days following administration of a monoamine oxidase inhibitor (MAOI). These drugs are also contraindicated in patients with glaucoma.

Stimulants are contraindicated in patients with marked anxiety or agitation as these symptoms may be aggravated.

Amphetamines are contraindicated in patients with advanced arteriosclerosis, symptomatic cardiovascular disease, moderate to severe hypertension, hyperthyroidism, or a history of drug abuse.

Methylphenidate (Methylin, Metadate ER, Metadate CD, Ritalin, Ritalin LA, Ritalin-SR, Concerta, Daytrana, Quillivant XR), and dexmethylphenidate (Focalin, Focalin XR) are contraindicated in patients with tics or a diagnosis or family history of Tourette's syndrome.

Quillivant XR is contraindicated with known hypersensitivity to methylphenidate or product components.

Atomoxetine (Strattera) is contraindicated in patients with severe cardiac or vascular disorders whose condition would be expected to deteriorate with clinically significant increases in blood pressure or heart rate. Increases in blood pressure and heart rate, orthostasis, and syncope have been reported. Atomoxetine should be used with caution in patients with hypertension, tachycardia, or cardiovascular or cerebrovascular disease.

Clonidine ER and guanfacine ER are contraindicated in patients with a history of hypersensitivity to products containing those ingredients.

Modafinil (Provigil) and armodafinil (Nuvigil) are contraindicated in patients with known hypersensitivity to modafinil or armodafinil or their inactive ingredients.

Warnings

Stimulants have boxed warnings regarding the high potential for abuse. Prolonged use of these agents can lead to drug dependence. Misuse of amphetamines may cause sudden death and serious cardiovascular adverse events; use of approved doses of MPH has an increased risk of sudden death due to cardiac events in adults and children that have pre-existing cardiac comorbidities. Patients should be carefully supervised during withdrawal from MPH and dexmethylphenidate as it may result in depression and/or unmasking of symptoms.

Stimulants should be used with caution in patients with pre-existing psychosis, bipolar disorder, or aggression as these conditions may be exacerbated. Modafinil and armodafinil have also been reported to induce mania, delusions, hallucinations, suicidal ideations, and aggression in patients with and without prior history of psychiatric illness. Two cases of suicide ideation were observed in clinical trials with armodafinil. Treatment-emergent psychotic or manic symptoms have been reported in 0.1 percent of patients receiving stimulants and 0.2 percent of patients receiving atomoxetine (Strattera).

Sudden death has been reported in association with stimulants and with atomoxetine at usual doses in children and adolescents with structural cardiac abnormalities or other serious heart problems. Stimulants and atomoxetine generally should not be used in patients with known serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, or other serious cardiac problems that may place them at increased vulnerability to the noradrenergic effects of atomoxetine. In addition, stimulants and atomoxetine can cause increased blood pressure and heart rate. Caution is indicated in treating patients with pre-existing hypertension, heart failure, recent myocardial infarction, or ventricular arrhythmia. Pulse and blood pressure should be monitored at baseline and during therapy.

Stimulants may cause long-term suppression of growth.

Stimulants may lower the seizure threshold and may cause visual disturbances.

Stimulants have been associated with peripheral vasculopathy, including Raynaud's phenomenon.

Painful and prolonged penile erections and priapism have been reported with atomoxetine, mixed amphetamine salts, dextroamphetamine, methamphetamine, lisdexamfetamine, methylphenidate, and dexmethylphenidate products. Priapism was not reported with drug initiation but developed after some time on the drug, often subsequent to a dosage increase. Priapism has also appeared during a period of drug withdrawal (e.g., drug holidays or during discontinuation). Immediate medical attention should be sought if signs or symptoms of painful or prolonged penile erections or priapism are observed.

Rare cases of GI obstruction have been reported with nondeformable controlled-release formulations similar to MPH OROS (Concerta).

Use of MPH transdermal system (Daytrana) may lead to contact sensitization as evidenced by allergic contact dermatitis. MPH transdermal system should be discontinued if this occurs. Patients may

develop systemic sensitization or other systemic reactions to MPH-containing products given via other routes. It is possible that some patients sensitized to MPH may not be able to take MPH in any form.

Limited reports of multi-organ hypersensitivity reactions have been reported after initiation of treatment between four to 33 days in patients taking modafinil. Some of the presenting signs and symptoms for the disorder were fever, rash, pruritus, asthenia, myocarditis, hepatitis, liver function test abnormalities, and dermatological abnormalities. A similar risk of multi-organ hypersensitivity reactions with armodafinil cannot be ruled out.

Rare cases of serious rash, such as Stevens-Johnson syndrome, toxic epidermal necrolysis, and drug rash with eosinophilia and systemic symptoms, have occurred in patients taking modafinil and armodafinil. The cases reported have occurred within one to five weeks after initiating drug treatment, and predictors to occurrence of rash are not known. Rare cases of serious rash, including Stevens-Johnson syndrome and drug rash, have occurred in pediatric patients taking armodafinil, as well.

Atomoxetine has a boxed warning regarding the increased risk of suicidal ideation in children and adolescents. In a combined analysis of 12 short-term placebo-controlled trials of over 2,200 patients, suicidal ideation occurred in approximately 0.4 percent of patients compared with no patients receiving placebo. All occurrences were reported during the first month of treatment in children 12 years and younger. Monitoring, including face-to-face contact with patients or caregivers, should occur weekly during the first four weeks of treatment, then every other week for four weeks, then again at 12 weeks.

Patients on atomoxetine should be monitored for the appearance or worsening of aggressive behavior or hostility.

Atomoxetine has a warning regarding severe liver injury; rare, but marked, elevations of hepatic enzymes and bilirubin have been reported. In two case reports, liver injury resolved after discontinuation of atomoxetine (with concomitant immunosuppressive therapy in one case).[120] The manufacturer warns to discontinue atomoxetine permanently in patients with any sign of jaundice or hepatic lab abnormality; other treatment options should be considered.

Dose-dependent decreases in blood pressure and heart rate have been seen in patients using clonidine ER or guanfacine ER. Heart rate and blood pressure should be measured prior to initiation of therapy, following dose increases, and periodically while on therapy. Use with caution in patients with a history of hypotension, heart block, bradycardia, cardiovascular disease, or syncope. The sympatholytic action of clonidine ER may worsen sinus node dysfunction and atrioventricular (AV) block, especially in patients taking other sympatholytic drugs. Advise patients to avoid becoming dehydrated or overheated.

In 2011, the FDA published a safety communication based on studies that evaluated heart attacks and sudden deaths including children, adolescents, and adults treated with ADHD medications, and a study that assessed strokes in these adults.[121,122] The FDA concluded that no increase in risk of serious adverse cardiovascular events in patients treated with ADHD medications was found. The medications studied include stimulants, atomoxetine, and pemoline (no longer marketed).

To avoid adverse effects on blood pressure when discontinuing therapy, the clonidine ER or guanfacine ER dose should generally be tapered off. Clonidine ER decrements should not exceed 0.1 mg every three to seven days. For guanfacine ER, decrease in decrements of no more than 1 mg every three to seven days.

All stimulants used to treat ADHD are associated with peripheral vasculopathy, including Raynaud's phenomenon. Signs and symptoms generally improve after reduction in dose or discontinuation of the drug. Monitor for digital changes during treatment with ADHD stimulants.

Risk Evaluation and Mitigation Strategies (REMS)

The REMS requirements for armodafinil and modafinil were eliminated in 2012.

DRUG INTERACTIONS

Gastrointestinal (e.g., antacids) and urinary (e.g., acetazolamide, some thiazides) alkalinizing agents increase blood levels and activity of amphetamines. Gastrointestinal (e.g., ascorbic acid) and urinary (e.g., ammonium chloride) acidifying agents decrease absorption and activity of the amphetamines. Proton pump inhibitors reduce gastric acidity; patients who co-administer them with amphetamines should be monitored for changes in clinical effect due to the potential for decreases in the time to maximum concentration of amphetamine products.

Effects can be additive when stimulants are used concurrently with other psychostimulants or sympathomimetics.[123,124,125] Due to the potential for excessive CNS or cardiovascular stimulation, combination use should be avoided unless necessary, and, if unavoidable, then used with caution.[126] In general, the concurrent use of MPH (Methylin, Metadate ER, Metadate CD, Quillivant XR, Ritalin, Ritalin LA, Ritalin-SR, Concerta, Daytrana) with amphetamines is not recommended. [127] Since there are no clinical data regarding the concurrent use of MPH and atomoxetine (Strattera), concurrent use should be avoided.[128]

Amphetamine may stimulate the release of serotonin in the CNS and thus may interact with other serotonergic agents, such as the serotonin receptor agonists. These interactions could lead to serotonin excess, which could increase the risk of serotonin syndrome occurring.[129] Melatonin may exacerbate the monoaminergic effects of amphetamine-related medications. Coadministration of melatonin with methamphetamine (Desoxyn) in animal studies resulted in increased dopaminergic and serotonergic stimulation.[130]

Lithium may antagonize the central stimulating effects of amphetamines and should be avoided.[131, 132] Likewise, MPH should not be used concurrently with lithium since this may alter the effects of these agents on the underlying mood disorder. Stimulant medications occasionally worsen mania.[133,134] Haloperidol and chlorpromazine also inhibit the central stimulant effects of the amphetamines.

MPH and dexmethylphenidate may inhibit the metabolism of coumarin anticoagulants, anticonvulsants (e.g., phenobarbital, phenytoin, primidone), and some antidepressants (tricyclics and selective serotonin reuptake inhibitors). Downward dose adjustment of these drugs may be required when given concomitantly with MPH.

Like the MAOIs, stimulants and atomoxetine potentiate the effects of catecholamine neurotransmitters.[135] MAOIs or drugs that possess MAOI activity, such as procarbazine, can prolong and intensify the cardiac stimulation and vasopressor effects of the stimulants. Stimulants and atomoxetine should not be administered during or within 14 days following the use of MAOIs or drugs with MAO-inhibiting activity. [136,137,138]

Caution should be used when guanfacine ER (Intuniv) is administered to patients taking strong CYP3A4/5 inhibitors (e.g., ketoconazole), which can cause a substantial increase in rate and extent of

guanfacine exposure (AUC) leading to an increased risk of adverse events such as hypotension, bradycardia, and sedation.[139]

Concomitant use of guanfacine ER with a CYP3A4 inducer (e.g., rifampin) can cause a significant decrease in the rate and extent of guanfacine exposure (AUC).[140] An increase in the dose of guanfacine ER within the recommended dose range may be considered.

Coadministration of guanfacine and valproic acid can result in increased concentrations of valproic acid. Adjustments in the dose of valproic acid may be required.[141]

Somnolence and sedation with guanfacine ER and clonidine ER were commonly reported adverse reactions in clinical studies, especially during initial use.[142] Caution should be used when operating heavy equipment or driving and use with other CNS depressants, including alcohol. Furthermore, alcohol should be avoided while taking methylphenidate.

Likewise, drugs affecting sinus node function or AV nodal conduction or antihypertensive drugs have the potential for additive effects when used with clonidine. Serious adverse events have been reported during concomitant use of MPH and clonidine; no causality has been established.

Use of modafinil (Provigil) with other psychostimulants has not been extensively studied, and concurrent use is not recommended. Coadministration of amphetamine and modafinil may increase stimulant-associated side effects.[143,144] Single-dose studies of MPH combined with modafinil showed that the rate of absorption of modafinil was delayed up to one hour in the presence of MPH. No changes occurred in the metabolism and extent of absorption of either medication.

Armodafinil (Nuvigil) and modafinil have not been evaluated for interactions with drugs with MAOI activity.[145] Until more is known regarding the pharmacology of modafinil, it may be prudent to caution against the use of these agents in the presence of a MAOI.

Armodafinil and modafinil moderately induce CYP3A activity. Drugs that are substrates for CYP3A4/5, such as cyclosporine, may require dosage adjustment. Armodafinil and modafinil moderately inhibit CYP2C19 activity. Drugs that are substrates for CYP2C19, such as omeprazole, may require dosage reduction.

The effectiveness of steroidal contraceptive may be reduced with concurrent use of either armodafinil or modafinil and for one month after discontinuation of therapy. Alternative or concomitant methods of contraception are recommended and for one month after discontinuation of armodafinil or modafinil.

Where data specific to armodafinil drug interactions are not available, any available information on modafinil should be applicable to armodafinil, according to the prescribing information.

ADVERSE EFFECTS

For the most part, adverse effects of stimulants are dose-dependent, mild to moderate in severity, and diminish with alteration of medication dose or timing.[146] They commonly subside spontaneously during the first one to two weeks of treatment.[147] Nonetheless, the majority of children treated with stimulants do experience some adverse effects, and these adverse effects are often the reason stimulant treatment is discontinued.[148,149]

In a double-blind study, investigators found that based on parent assessment, only two adverse effects were more prevalent after initiation of stimulants than prior to initiation. These were insomnia

(dextroamphetamine) and poor appetite (dextroamphetamine and MPH).[150] Investigators also found that the severity of several adverse effects (insomnia, irritability, crying, anxiousness, sadness/unhappiness, and nightmares) was higher in dextroamphetamine than in MPH; there were no adverse effects with higher severity in MPH than in dextroamphetamine.

In 2001, the American Academy of Pediatrics released a policy statement indicating that adverse effects of stimulant medications are usually mild and of short duration, and there is no significant impairment of height in adult life. The guidelines state that stimulants used for ADHD do not require routine serologic, hematologic, or electrocardiogram monitoring.[151]

Most side effects associated with stimulants, such as decreased appetite, headaches, stomachaches, insomnia, nervousness, and social withdrawal, can usually be managed by adjusting the dosage and/or timing of administration. For instance, administering stimulants with or after meals can reduce appetite suppression. Moving the last daily dose to an earlier time can reduce insomnia. If children are on too high of a dosage or are overly sensitive to the stimulants, the agents may cause them to be over focused or appear dull or overly restricted. Lowering the dosage of medication or changing to a different medication can usually reduce the effects.

Long-term use of stimulant therapy has not demonstrated any obvious ill effects through observational data; there are no formal long-term studies.

In general, a review of the evidence shows no statistically significant differences in the incidence of adverse effects between immediate-release and extended-release formulations. There is no evidence to support statistically significant differences with respect to adverse effects of dextroamphetamine (Dexedrine, Zenzedi, Procentra) and MPH (Methylin, Metadate ER, Metadate CD, Quillivant XR, Ritalin, Ritalin LA, Ritalin-SR, Concerta, Daytrana).

Adverse Effects in Children (*Adults Only)

Drug	Headache	Abdominal pain	Anorexia	Insomnia
Stimulants: Immediate-Release				
armodafinil (Nuvigil)*[152]	17 (9)	2 (1)	1 (0)	5 (1)
dexmethylphenidate (Focalin)[153]	nr	15 (6)	6 (1)	nr
dextroamphetamine IR (Zenzedi)[154]	reported	reported*	reported	reported
dextroamphetamine solution (Procentra)[155]	reported	nr	reported	reported
methamphetamine (Desoxyn)[156]	reported	nr	nr	reported
methylphenidate IR (Methylin, Ritalin)[157]	reported	reported	reported	reported
mixed salt amphetamines IR (Adderall)[158]	reported	nr	reported	reported
modafinil (Provigil)*[159]	34 (23)	1 (≥1)	4 (1)	5 (1)
Stimulants: Extended-Release				
dexmethylphenidate (Focalin XR)[160]	25 (11)	nr	30 (9)	reported
dextroamphetamine ER (Dexedrine)[161]	reported	nr	reported	reported
lisdexamfetamine (Vyvanse)[162]	reported	12 (6)	5 (0)	13-23 (3-4)
methylphenidate ER (Metadate ER)[163]	reported	reported	reported	reported
methylphenidate ER (Quillivant XR)[164]	nr	reported	reported	reported
methylphenidate ER OROS (Concerta)[165]	<1	6.2 (3.8)	<1	2.8 (0.3)
methylphenidate ER (Metadate CD)[166]	12 (8)	7 (4)	9 (2)	5 (2)
methylphenidate ER (Ritalin LA)[167]	>5 (nr)	>5 (nr)	>5 (nr)	>5 (nr)
methylphenidate transdermal (Daytrana)[168]	12.4-15.3 (11.8-12.5)	4.8-7.1 (0-5.9)	4.8-5.1 (1.2-1.4)	6.2-13.3 (2.8-4.7)
mixed salt amphetamines (Adderall XR)[169]	reported	11-14 (2-10)	22 (2)	12-17 (2-4)
Non-Stimulants				
atomoxetine (Strattera)[170]	19 (15)	18 (10)	3 (1)	≥2 (nr)
clonidine ER (Kapvay)[171]	19-29 (18)	13-20 (17)	nr	4-6 (1)
guanfacine ER (Intuniv)[172]	21-24 (13-19)	10-11 (3-9)	5-7 (3-4)	12 (6)

Adverse effects are reported as a percentage. Adverse effects data are obtained from prescribing information and are not meant to be comparative or all inclusive. Incidences for the placebo group are indicated in parentheses. nr = not reported

*Zenzedi adverse event reported as gastrointestinal disturbance

Other side effects common to the stimulants include irritability, flattened affect, social withdrawal, weepiness, mood lability, tremor, weight loss, and reduced growth velocity.

The majority of patients in the pivotal phase III clinical trial of MPH transdermal (Daytrana) had minimal to definite erythema. Erythema generally caused little discomfort and did not usually result in discontinuation from treatment. However, use of MPH transdermal may lead to contact sensitization and should be discontinued if contact sensitization is suspected. Patients sensitized from use of MPH transdermal may develop systemic sensitization or other systemic reactions if methylphenidate-containing products are taken via other routes (e.g., orally). The most common adverse reactions with the extended-release suspension (Quillivant XR) reported in the Phase 3 controlled study conducted in 45 ADHD patients (ages six to 12 years) were affect lability, excoriation, initial insomnia, tic, decreased appetite, vomiting, motion sickness, eye pain, and rash.

Stimulants can cause unpredictable motor tics, which transiently occur in 15 to 30 percent of children. Tics may appear in some patients when they are on stimulant medication and disappear with discontinuation of the medication. Fifty percent of patients with Tourette's disorder also have ADHD which may present two or three years before the tics appear. It is believed that stimulants do not cause Tourette's disorder, but simply unmask the disorder. Motor and verbal tics have not been associated with atomoxetine (Strattera).[173]

Paresthesia (including formication) has been associated with treatment on mixed amphetamine salts (Adderall, Adderall XR).

Effects on Growth

The 2011 American Academy of Pediatrics Clinical Practice Guideline for the School Aged Child with ADHD acknowledges that appetite suppression and weight loss are common adverse effects of stimulants, but studies of stimulant use have found little or no decrease in expected height; any decrease in growth early in treatment is later compensated.[174] A temporary slowing in growth rate (2 cm less growth in height and 2.7 kg less increase in weight over three years) has been noted in children starting treatment with MPH at ages seven through 10 years.

With stimulants, delayed growth may be a concern through mid-adolescence but normalizes by late adolescence. This appears to be an effect of the ADHD and not its treatment; however, there have been reports of decreased growth with continuous stimulant treatment. Drug holidays can be used, but the benefits of this strategy in mitigating growth delays have not been demonstrated in a controlled setting.

Over 18 months, patients on atomoxetine were reported to gain weight (average 6.5 kg) and height (average 9.3 cm), although there was a net loss in mean weight and height percentile points. Mean weight decreased from the 68th to 60th percentile, and mean height decreased from the 54th to 50th percentile. Attenuation of the effects on growth occurs by 24 months.[175]

SPECIAL POPULATIONS[176,177,178,179,180,181,182,183,184,185,186, 187,188,189,190]

Pediatrics

Methamphetamine (Desoxyn), MPH (Concerta, Methylin, Metadate CD, Metadate ER, Quillivant XR, Ritalin, Ritalin LA, Daytrana), d-MPH (Focalin, Focalin XR), mixed amphetamine salts ER (Adderall XR), lisdexamfetamine (Vyvanse), and atomoxetine (Strattera) are indicated for children six years of age and older. Dextroamphetamine ER (Dexedrine) is indicated for children five years of age and older. Some of the immediate-release stimulants, dextroamphetamine IR tablets (Zenzedi) and solution (Procentra) and mixed amphetamine salts (Adderall), are indicated for children as young as three years. The prescribing information for the drugs in this class used for the treatment of ADHD include a warning about using the drugs in children younger than the indicated age, but there are some data on the use of these drugs in younger children.

The safety and efficacy of guanfacine ER (Intuniv) in pediatric patients less than six years of age have not been established. For children and adolescents six years and older, efficacy beyond nine weeks and safety beyond two years of treatment have not been established.

The safety and efficacy of clonidine ER (Kapvay) in ADHD patients less than six years of age have not been established. Maintenance therapy beyond five weeks has not been evaluated; patients should be periodically re-evaluated to determine the long-term usefulness of clonidine ER.

Safety and effectiveness in patients below the age of 16 years for modafinil (Provigil) and 17 years for armodafinil (Nuvigil) have not been established. Serious rash has been reported in pediatric patients receiving these agents.

Children under three years of age – Numerous studies indicate that stimulants are effective in the treatment of ADHD in preschool children.[191,192] Although, some have expressed concern that the use of neuropsychiatric drugs in children in this age group could have long term effects on neurotransmitters in the brain.[193] The 2004 American Academy of Child and Adolescent Psychiatry (AACAP) guidelines recommend initial parent training and a structured preschool setting that may progress to low-dose medication with frequent monitoring. Behavior modification therapy may be useful if implemented consistently. The AACAP suggests medication use only in the most severe cases, or where parent training and/or school placement are unavailable or unsuccessful. If medications are used, the AACAP suggests daily treatment without weekend holidays.

Pregnancy

Guanfacine ER is Pregnancy Category B. All other agents in this class are Pregnancy Category C.

Hepatic Impairment

For patients with moderate (Child-Pugh Class B) hepatic impairment, the initial and target doses of atomoxetine (Strattera) should be reduced by 50 percent. For patients with severe (Child-Pugh Class C) hepatic impairment, the initial and target doses should be reduced by 75 percent. For patients taking strong CYP2D6 inhibitors (e.g., paroxetine, fluoxetine, quinidine) or in patients who are known to be CYP2D6 poor metabolizers, atomoxetine should be started at 0.5 mg/kg/day and only increased to the usual target dose of 1.2 mg/kg/day if symptoms fail to improve after four weeks and the initial dose is well tolerated.

For patients with severe hepatic impairment, the dosage of modafinil (Provigil) should be reduced by 50 percent. The bioavailability of the inactive metabolite, modafinil acid, is increased nine-fold in patients with severe renal impairment (CrCl ≤20 mL/min); safety and efficacy of modafinil in this patient group have not been determined.

The dose of armodafinil (Nuvigil) should be reduced in patients with severe hepatic impairment. There is inadequate information to determine safety and efficacy of dosing in patients with severe renal impairment.

DOSAGES

Drug	Ages	Usual Initial Dosage	Maximum Dosage	Dosage Forms
Stimulants: Immediate-Release				
armodafinil (Nuvigil®)[194]*	≥17 years	150 mg to 250 mg once daily in the morning	250 mg per day	Tablets: 50, 150, 200, 250 mg
dexmethylphenidate (Focalin)[195]	≥6 years	2.5 mg twice daily	10 mg twice daily	Tablets: 2.5, 5, 10 mg
dextroamphetamine IR (Zenzedi)[196]	3-5 years	2.5 mg once daily	40 mg per day	Tablets: 5, 10 mg Tablets (Zenzedi): 2.5, 5, 7.5, 10, 15, 20, 30 mg
	≥6 years	5 mg once or twice daily	40 mg/day in two or three divided doses	
dextroamphetamine solution (Procentra)[197]	3-5 years	2.5 mg once daily	40 mg per day	Oral solution: 5 mg/5 mL
	≥6 years	5 mg once or twice daily	40 mg per day	
methamphetamine (Desoxyn)[198]	≥6 years	5 mg once or twice daily	20-25 mg/day in two divided doses	Tablets: 5 mg
methylphenidate IR (Methylin, Ritalin)[199]	≥6 years	5 mg twice daily	60 mg/day in two or three divided doses	Tablets: 5, 10, 20 mg Chewable tablets: 2.5, 5, 10 mg Oral solution: 5 mg/5 mL, 10 mg/5 mL
mixed amphetamine salts IR (Adderall)[200]	3-5 years	2.5 mg once daily	40 mg/day in two or three divided doses	Tablets: 5, 7.5, 10, 12.5, 15, 20, 30 mg
	≥6 years	5 mg two or three times daily		
modafinil (Provigil®)[201]*	≥17 years	200 mg once daily in the morning	400 mg per day	Tablets: 100, 200 mg

Dosages

Drug	Ages	Usual Initial Dosage	Maximum Dosage	Dosage Forms
Stimulants: Extended-Release				
dexmethylphenidate ER (Focalin XR)[202]	6-17 years	5 mg once daily	30 mg per day	Capsules: 5, 10, 15, 20, 25, 30, 35, 40 mg
	≥18 years (adults)	10 mg once daily	40 mg per day	
dextroamphetamine ER (Dexedrine)[203]	5-11 years	Total daily IR dosage given once daily	45 mg once daily	Capsules: 5, 10, 15 mg
	≥6 years	Total daily IR dosage given once daily	60 mg once daily	
lisdexamfetamine (Vyvanse)[204]	≥6 years	30 mg daily in the morning	70 mg daily in the morning	Capsules: 20, 30, 40, 50, 60, 70 mg
methylphenidate ER (Metadate ER)[205]	≥6 years	20-60 mg/day in one or two divided doses	60 mg/day in one or two divided doses	Tablets: 20 mg
methylphenidate ER OROS (Concerta)[206]	6-12 years	18 mg once daily	54 mg once daily	Tablets: 18, 27, 36, 54 mg
	13-17 years	18 mg once daily	72 mg once daily (≤2 mg/kg/day)	
	18-65 years (adults)	18 or 36 mg once daily	72 mg once daily	
methylphenidate ER (Metadate CD)[207]	≥6 years	20 mg once daily	60 mg once daily	Capsules: 10, 20, 30, 40, 50, 60 mg
methylphenidate ER (Quillivant XR)[208]	≥6 years	20 mg once daily	60 mg once daily	Suspension: 300 mg/60 mL, 600 mg/120 mL, 750 mg/150 mL, 900 mg/180 mL (5 mg/ mL)
methylphenidate ER (Ritalin LA)[209]	≥6 years	20 mg once daily	60 mg once daily	Capsules: 10, 20, 30, 40 mg
methylphenidate transdermal (Daytrana)[210]	≥6 years	10 mg patch worn nine hours daily	30 mg patch worn nine hours daily	Patches: 10, 15, 20, 30 mg per 9 hours
mixed amphetamine salts ER (Adderall XR)[211]	6-17 years	5-10 mg once daily	30 mg once daily	Capsules: 5, 10, 15, 20, 25, 30 mg
	≥18 years (adults)	20 mg once daily	20 mg once daily	
Non-Stimulants				
atomoxetine (Strattera)[212]	≥6 years and ≤70 kg	0.5 mg/kg/day in one or two divided doses	1.4 mg/kg/day in one or two divided doses	Capsules: 10, 18, 25, 40, 60, 80, 100 mg
	≥6 years and ≥70 kg and adults	40 mg/day in one or two divided doses	100 mg/day given in one or two divided doses	
clonidine ER (Kapvay)[213]	6-17 years	0.1 mg at bedtime	0.2 mg twice daily	Tablets: 0.1 mg Dosepak: 3 blister cards of 20 tablets; each card containing 10 tablets of 0.1 mg and 10 tablets of 0.2 mg
guanfacine ER (Intuniv)[214]	6-17 years	1 mg once daily in the morning or evening	4 mg once daily in the morning or evening	Tablets: 1, 2, 3, 4 mg

* Nuvigil and Provigil are not approved for ADHD treatment and are only approved to treat circadian rhythm disruption, narcolepsy, and sleep apnea.

The contents of lisdexamfetamine (Vyvanse) capsules can be emptied and mixed into a glass of water. A spoon may be used to break apart any compacted powder in the water. The content should be stirred until completely dispersed. The active ingredient dissolves completely once dispersed; however, a film containing the inactive ingredients may remain in the glass once the water is consumed.

MPH immediate-release (Methylin, Ritalin) should be administered 30 to 45 minutes before meals. Dexmethylphenidate (Focalin, Focalin XR) and MPH extended-release can be administered without regard to meals. The timing of the midday dose of MPH immediate-release and dexmethylphenidate immediate-release should be individualized based on patient response. The last daily dose of MPH extended-release should be given several hours before bedtime.

MPH transdermal patches (Daytrana) should be applied two hours prior to the desired onset of activity and should be worn for nine hours. Wear time can be individualized based on patient response.

Clonidine ER (Kapvay) doses should be increased at a frequency of 0.1 mg per week. Tablets should not be chewed, crushed, or split. Do not substitute clonidine ER for immediate-release clonidine on a milligram-for-milligram basis.

If switching from guanfacine IR to guanfacine ER (Intuniv), discontinue guanfacine IR and titrate with guanfacine ER according to the recommended dosing schedule.

Hypersomnolence

Armodafinil (Nuvigil 50, 150, 250 mg tablets) – for adults (≥17 years) with narcolepsy or obstructive sleep apnea/hypopnea syndrome, 150 or 250 mg is given once daily in the morning. For patients with shift work sleep disorder, 150 mg should be administered one hour prior to the start of the work shift.[215]

Dextroamphetamine (Zenzedi, Procentra) – for adults and adolescents, 5 mg twice daily titrated to a maximum of 60 mg/day in two or three divided doses; for children six to 12 years, 5 mg once daily titrated to maximum of 60 mg/day in two or three divided doses. Once the dosage has been stabilized, patients can be converted to an equivalent dosage of dextroamphetamine extended-release (Dexedrine) given once daily.

Methylphenidate (Ritalin, Methylin, Metadate ER, Ritalin SR) – dosages for the treatment of narcolepsy are the same as those for ADHD.

Mixed amphetamine salts (Adderall) - for the treatment of narcolepsy 5 mg to 60 mg per day in divided doses. The suggested initial dose for patients aged 6-12 years is 5 mg daily; dose may be titrated in increments of 5 mg per day at weekly intervals until optimal response is obtained. In patients 12 years of age and older, start with 10 mg daily and may titrated by 10 mg per day at weekly intervals until optimal response is obtained.

Modafinil (Provigil 100, 200 mg tablets) - for adults (≥16 years) with narcolepsy or obstructive sleep apnea/hypopnea syndrome, 200 mg is given once daily in the morning. For patients with shift-work sleep disorder, the dose should be administered one hour prior to work.

Obesity

For adjunctive treatment of obesity, methamphetamine (Desoxyn) 5 mg is administered before each meal. Treatment should last only a few weeks.

CLINICAL TRIALS

Articles were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the use of all drugs in this class. Randomized, controlled, comparative trials are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question, and include follow-up (endpoint assessment) of at least 80 percent of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship and/or funding must be considered, the studies in this review have also been evaluated for validity and importance.

Studies of ADHD of less than four weeks' duration were excluded as it is generally accepted that it takes at least this long to adequately titrate to the optimal dosage of a given agent. Studies conducted more than 25 years ago were excluded, primarily due to a lack of well-controlled clinical trials from that time period. Many of these older studies verified the effectiveness of the stimulants available at that time in treating the symptoms of ADHD.

Attention-deficit/Hyperactivity Disorder (ADHD)

Rating Scales

Specific

- Conners' Parent Rating Scale (CPRS) – The scale provides the parents' or caregivers' perspective on a child's behavior. The scale is 92 percent sensitive and 94 percent specific.
- Swanson, Nolan, and Pelham scale (SNAP) – The scale has been shown to have greater than 94 percent sensitivity and specificity in distinguishing hyperactive, inattentive, and impulsive children with ADHD from those without ADHD based on DSM-III-R criteria.
- ADHD Rating Scale-IV (ADHD RS) – The scale, which can be completed by a parent, teacher, or clinician, is less effective than the SNAP in differentiating children with ADHD from those without ADHD. It has been shown to have good internal consistency and test-retest reliability. The parent form is 84 percent sensitive and 49 percent specific; the teacher form is 72 percent sensitive and 86 percent specific.

Global

Broad-band scales are not useful as tools to detect clinical-level problems in children presenting; they have low sensitivities and specificities of 70 to 80 percent.

- CGI-I – Clinical Global Impression improvement subscale
- CGI-S - Clinical Global Impression severity subscale
- C-GAS – Children's Global Assessment Scale

atomoxetine (Strattera) versus MPH immediate-release

Two identical 12-week double-blind trials were conducted in 291 children (ages seven to 13 years) with ADHD.[216] Stimulant-naïve patients were randomized to atomoxetine (up to 2 mg/kg/day or 90 mg), MPH (up to 1.5 mg/kg/day, or 60 mg) or placebo. Patients with prior stimulant exposure were randomized only to atomoxetine or placebo. Atomoxetine significantly reduced ADHD RS total scores, the primary endpoint, compared with placebo in each study ($p<0.001$). Changes in the CGI-S and CPRS also showed atomoxetine to be significantly superior to placebo in reducing ADHD symptoms. There was no significant difference between atomoxetine and MPH. A subsequent subanalysis of 51 female subjects showed that atomoxetine was similarly superior to placebo in this patient subset.[217]

atomoxetine (Strattera) versus MPH OROS (Concerta)

A randomized, double-blind, placebo-controlled study compared the response, as measured by the ADHD Rating Scale of atomoxetine, MPH OROS, and placebo.[218] A total of 516 children ages six to 16 years with ADHD were randomized to receive 0.8-1.8 mg/kg per day of atomoxetine (n=222), 18-54 mg/day of MPH OROS (n=220), or placebo (n=74) for six weeks. Patients who had previously had an inadequate response to stimulant treatment were excluded from the study. After six weeks, using double-blind conditions, the patients receiving MPH OROS were switched to atomoxetine. Response was determined by a 40 percent reduction from baseline as measured by the ADHD Rating Scale. Response results indicated that atomoxetine and MPH OROS were better than placebo, with atomoxetine resulting in a 45 percent response, MPH OROS resulting in a 56 percent response, and placebo resulting in a 24 percent response. The response rate for MPH OROS was significantly higher than atomoxetine ($p=0.016$). Seventy patients who received MPH OROS did not respond, but 30 of these patients (43 percent) responded after being switched to atomoxetine. Also, note that 69 patients did not respond to atomoxetine treatment, but 29 (42 percent) of these patients previously responded to MPH OROS treatment. Completion and discontinuations rates due to adverse events were low and similar for all treatment groups. Results indicated that response to MPH OROS was greater than atomoxetine, but patients not responding to MPH OROS initially may respond to atomoxetine treatment instead. Both agents had a superior response rate over placebo.

atomoxetine (Strattera) versus MPH immediate-release

A randomized, double-blind, crossover trial compared the efficacy of atomoxetine and MPH for treating ADHD, as well as their effects on the sleep of children with ADHD.[219] Eighty-five children with ADHD, either in a private practice setting or a hospital setting, were given twice daily atomoxetine (mean dose 42.29 mg/day) and three times daily MPH (mean dose 58.27 mg/day), each for approximately seven weeks. Relative to baseline, actigraphy data indicated that MPH increased sleep latency significantly more than did atomoxetine (39.2 versus 12.1 minutes; $p<0.001$); these results were consistent with polysomnography data. Compared with MPH, child diaries indicated that taking atomoxetine had less sleep disturbance adverse effects. For example, it was easier to wake up in the morning, took less time to fall asleep, and the patients recorded better sleep with atomoxetine treatment. Parents reported similar findings such as the children were less irritable, had fewer difficulties with waking in the morning, and were less resistant at night to prepare for bed when administered atomoxetine as opposed to MPH. Using the main measures of efficacy, the medications had similar efficacy for treatment of ADHD. Greater incidence of decreased appetite and insomnia with MPH were the only significant differences in treatment-emergent adverse events. Both medications decreased nighttime awakenings, but the decrease was greater for MPH.

clonidine ER (Kapvay) versus placebo

The efficacy of clonidine ER in the treatment of ADHD was established in two manufacturer approval trials in pediatric patients with ADHD ages six to 17 years.[220] Signs and symptoms of ADHD were evaluated using the ADHD RS-IV total score including hyperactive/impulsivity and inattentive subscales. Study 1 was a randomized, double-blind, placebo-controlled, study of 236 patients who were randomly assigned to clonidine ER 0.2 mg or 0.4 mg daily or placebo daily. At both doses, improvements in ADHD symptoms were statistically significantly superior in clonidine ER patients compared with placebo patients at the end of five weeks as measured by the ADHD RS-IV total score. Study 2 was a randomized, double-blind, placebo-controlled, study in 198 pediatric patients. Patients had previously been treated with methylphenidate or amphetamine for four weeks with inadequate response. Patients were randomly assigned to clonidine ER as adjunct to the stimulant or the previous stimulant alone. The clonidine ER dose was initiated at 0.1 mg daily and titrated upward, as clinically appropriate. ADHD symptoms were statistically significantly improved in clonidine ER plus stimulant group compared with the stimulant-alone group at the end of five weeks as measured by the ADHD RS-IV total score.

guanfacine ER (Intuniv) versus placebo

The efficacy of guanfacine ER in the treatment of ADHD was evaluated in two placebo-controlled trials in children and adolescents ages six to 17 years.[221] Study 1 evaluated guanfacine ER 2, 3, or 4 mg dosed once daily in an eight-week, double-blind, placebo-controlled, parallel-group (n=345) trial. Study 2 evaluated guanfacine ER 1, 2, 3, or 4 mg dosed once daily in a nine-week, double-blind, placebo-controlled, parallel-group (n=324) trial. Doses were titrated in increments of up to 1 mg/week. The mean reductions in ADHD RS scores at endpoint were statistically significantly greater for guanfacine ER compared to placebo for both studies. Due to the relatively small proportion of adolescent patients (ages 13-17 years) enrolled into these studies (approximately 25 percent), these data may not be sufficient to demonstrate efficacy in the adolescent subgroup. When evaluated regarding dose per body weight, clinically relevant improvements were observed beginning at doses in the range 0.05-0.08 mg/kg/day. In these studies, dosages were not optimized by body weight, and over half (55 percent) of the adolescent patients received doses of 0.01-0.04 mg/kg. The most commonly reported treatment-emergent adverse events were headache, somnolence, fatigue, upper abdominal pain, and sedation. Small to modest changes in blood pressure, pulse rate, and electrocardiogram parameters were observed but were not clinically meaningful.

mixed amphetamine salts ER (Adderall XR) versus MPH OROS (Concerta)

A randomized, double-blind, placebo-controlled study compared mixed amphetamine salts ER, MPH OROS, and placebo on ADHD neuropsychological functioning.[222] Adolescents (n=35, 19 males) with a diagnosis of ADHD completed three separate assessments (5 PM, 8 PM, 11 PM) on three different days and medications (mixed amphetamine salts ER, MPH OROS, placebo). Delayed Matching-to-Sample and Go/No-go (GNG) neuropsychological tests, which measure visual memory, attention span, and response inhibition, were used to evaluate outcomes. Neuropsychological functioning, as measured by commission errors, reaction time and recall accuracy, showed significant improvement when patients were taking MPH OROS as opposed to placebo. Results suggest that MPH OROS impacts both symptomatic behavior, as well as cognitive functioning, which have implications for both academic performance and daily functioning.

dexmethylphenidate (Focalin), MPH immediate-release, and placebo

In a randomized, double-blind study, 132 subjects received dexmethylphenidate, MPH, or placebo twice daily for four weeks, with titration of the dose based on weekly clinic visits.[223] The primary efficacy variable was change from baseline of Teacher SNAP to last study visit. Secondary efficacy measures included the change on Parent SNAP, CGI-I, and Math Test performance. Treatment with either dexmethylphenidate (p=0.0004) or MPH immediate-release (p=0.0042) significantly improved Teacher SNAP ratings compared with placebo. The dexmethylphenidate group showed significant improvements compared with placebo on the afternoon Parent SNAP (p=0.0003) and on the Math Test scores obtained at 6 PM. (p=0.0236). Improvement based on CGI-I occurred in 67 percent of patients on dexmethylphenidate and 49 percent of patients on MPH immediate-release. Both active treatments were well tolerated.

MPH immediate-release, MPH OROS (Concerta), and placebo

A double-blind, placebo-controlled, randomized, five-period crossover study in 49 healthy subjects with a history of light (occasional) recreational stimulant use was performed to evaluate the abuse-related subjective effects of MPH OROS with comparable doses of MPH immediate-release.[224] Patients were included in the study if they demonstrated a positive response to a 20-mg dose of dextroamphetamine and a negative placebo response. Patients were then randomized to receive single doses of placebo, 54 and 108 mg MPH OROS, and 50 and 90 mg MPH immediate-release. For each treatment, patients were observed for 24 hours to assess pharmacokinetics, pharmacodynamics, and safety. Both doses of MPH immediate-release produced statistically significant higher positive stimulant effects with respect to placebo for all measures (p<0.001). MPH OROS 108 mg also produced statistically significant differences from placebo (p<0.01), but the more commonly prescribed dose, MPH OROS 54 mg, did not produce significant differences from placebo. Overall, for comparable dose levels, MPH OROS produced lower positive and stimulant subjective effects than MPH immediate-release, and the lowest MPH immediate-release doses produced more of an effect than the highest of MPH OROS doses, showing that formulation may help reduce abuse potential.

In a multicenter, double-blind trial, 282 children (ages six to 12 years) with ADHD were randomized to receive MPH immediate-release 5, 10, or 15 mg three times daily, MPH OROS 18, 36, or 54 mg once daily, or placebo for 28 days.[225] Response, defined as >30 percent reduction from baseline IOWA Conners Oppositional/Defiance (O/D) score, occurred in 52, 59, and 26 percent of patients in the MPH immediate-release, MPH OROS, and placebo groups, respectively, as rated by parents (p<0.0001 for comparison of both active treatments to placebo). Teacher-rated response rates were 63, 68, and 43 percent, respectively (p<0.0107 for comparison of active treatments to placebo). The response rate for the two higher doses of MPH OROS (77 percent) was significantly higher than for MPH immediate-release based on parent ratings (p<0.05). Forty-eight percent of the placebo group discontinued study drug early compared with 14 percent and 16 percent in the MPH and OROS MPH groups, respectively.

MPH extended-release (Quillivant XR) and placebo

A total of 45 subjects (ages six to 12 years) were enrolled in this dose-optimized, randomized, double-blind, placebo-controlled, crossover laboratory school study. The purpose of this study was to determine the efficacy of extended-release (ER) suspension of MPH compared with placebo in the treatment of ADHD in children.[226] Following a four to six week open-label dose optimization phase, subjects received two weeks of double-blind treatment, one week of MPH ER suspension and one

week of placebo. Efficacy measures included Swanson, Kotkin, Agler, M-Flynn and Pelham (SKAMP) Rating Scale-Combined and Permanent Product Measure of Performance (PERMP) mathematics tests measured at pre-dose and at 0.75, 2, 4, 8, 10, and 12 hours post-dose on each laboratory classroom day. MPH ER suspension resulted in significant ($p<0.0001$) improvements in the SKAMP-Combined score at four hours post-dose (mean=7.12) as compared with placebo (mean=19.58) in the completers (n=39). Significant separation from placebo occurred at each time point tested with onset of action at 45 minutes post-dose and duration of efficacy extending to 12 hours post-dose. Adverse events and changes in vital signs following MPH ER suspension were generally mild and consistent with the known safety profile of MPH. MPH ER suspension effectively reduced symptoms of ADHD in children beginning at 45 minutes and continuing for 12 hours post-dose.

MPH OROS (Concerta), MPH transdermal (Daytrana), and placebo

In a double-blind study, 270 children (ages six to 12 years) with ADHD were randomized to one of three treatment arms: MPH OROS + placebo patch, MPH transdermal + placebo capsule, or placebo capsule + placebo patch.[227] The study consisted of a five-week dose-optimization phase followed by a two-week maintenance phase. At the conclusion of the study, the mean daily doses were 43.4 and 22.9 mg for the oral and transdermal dosage forms, respectively. The primary endpoint was the change in ADHD RS from baseline. A reduction in ADHD RS of at least 30 percent was observed in 66, 78, and 29 percent of patients receiving MPH OROS, MPH transdermal and placebo, respectively (p=NS for comparison of active treatments; $p<0.05$ for comparison of each active treatment to placebo). Reductions from baseline in both the hyperactivity/impulsivity and the inattentiveness subscales were similar in both active treatment groups and were significantly greater than in the placebo group. The manufacturers of MPH transdermal funded the study.

lisdexamfetamine dimesylate (Vyvanse) versus placebo

A phase III, multicenter, randomized, double-blind, forced-dose, parallel-group study was conducted at 40 centers across the United States.[228] The purpose of the study was to assess the efficacy and tolerability of lisdexamfetamine in school-aged children with ADHD treated in the community, and to characterize the duration of action of lisdexamfetamine compared with placebo. The study included 290 randomized patients; 230 patients completed the study. Sixty patients did not complete the study mostly due to either lack of efficacy or adverse effects. Significant improvements in ADHD RS-IV scores were seen with all doses (30, 50, or 70 mg) of lisdexamfetamine compared with placebo, and in CPRS scores with all lisdexamfetamine doses versus placebo throughout the day. Efficacy was observed by the first week of treatment, and improvements were observed throughout the day up to about 6:00 p.m. The most frequently reported adverse effects among patients receiving lisdexamfetamine were typical of amphetamine products. Most adverse effects were mild to moderate and occurred in the first week.

A multi-center, randomized, double-blind, placebo-controlled, crossover design, modified analog classroom study of lisdexamfetamine to simulate a workplace environment in 142 adults who met Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV-TR) criteria for ADHD.[229] There was a four-week open-label, dose optimization phase with lisdexamfetamine (30, 50, or 70 mg/day in the morning). Subjects were then randomized to one of two treatment regimens: an optimized dose of lisdexamfetamine followed by placebo, each for one week, or placebo followed by lisdexamfetamine, each for one week. Efficacy assessments occurred at the end of each week, using the Permanent Product Measure of Performance (PERMP), a skill-adjusted math test that measures attention in ADHD. Lisdexamfetamine treatment, compared to placebo, resulted in a statistically significant improvement in

attention across all post-dose time points, as measured by average PERMP total scores over the course of one assessment day, as well as at each time point measured. The PERMP assessments were administered at pre-dose (-0.5 hours) and at 2, 4, 8, 10, 12, and 14 hours post-dose.

Hypersomnolence

Scales commonly used in the evaluation of hypersomnolence and its treatment includes:

- Epworth Sleepiness Scale (ESS) – This is a self-administered questionnaire that has been shown to provide a measurement of the subject's general level of daytime sleepiness.[230] This scale has a high level of internal consistency.[231]
- Maintenance of Wakefulness Test (MWT) – In the test, the subject sits in bed, resting against pillows in a quiet, dimly lit room, attempting to stay awake for 20 (or 40) minutes while under scrutiny and with electrodes and wires attached.[232]
- Multiple Sleep Latency Test (MSLT) – The test measures how quickly the subject falls asleep, when asked to do so, when lying down in a quiet, darkened bedroom while under scrutiny and with electrodes and wires attached.[233] The test is considered by many to be the gold standard for measuring daytime sleepiness, although analysis has recently shown it to be the least accurate of the three tests.[234,235]

modafinil (Provigil) versus placebo – narcolepsy

A total of 285 subjects between the ages of 18 and 68 years with a diagnosis of narcolepsy were enrolled in a randomized trial to receive modafinil 200 mg, modafinil 400 mg, or placebo once daily for nine weeks.[236] The mean ESS score was significantly lower for each modafinil treatment group compared to placebo at weeks three, six, and nine. Subjective sleepiness ratings at each evaluation were reduced from baseline in all three groups. At baseline, three percent of the modafinil 400 mg group, four percent of the modafinil 200 mg group, and three percent of the placebo group were able to remain awake for at least three Maintenance of Wakefulness Tests (MWTs). At week nine, the percentage of subjects able to stay awake for at least three tests significantly increased to 20 percent for the modafinil 400 mg group and 14 percent for the modafinil 200 mg group; no change occurred in the placebo group. Headache was reported to occur statistically significantly more often in the modafinil groups versus the placebo group. This study had an open-label treatment arm with demonstrated efficacy and safety for up to 40 weeks.

modafinil (Provigil) versus placebo – OSA-related daytime sleepiness

In a double-blind, parallel group, randomized study, investigators studied the efficacy and safety of modafinil verses placebo in 157 patients with OSA-related daytime sleepiness despite CPAP for a total of four weeks. [237] Patients were randomized to receive modafinil (n=77) at an initial dose of 200 mg per day during week one, then increasing over three weeks up to 400 mg per day, or placebo (n=80) once daily. Modafinil significantly improved daytime sleepiness, with significantly greater mean changes from baseline in ESS scores at weeks one and four ($p<0.001$), but not significantly different from placebo in MSLT at week four ($p<0.05$). The percentage of patients with normalized daytime sleepiness (ESS <10) was significantly higher with modafinil (51 percent) than with placebo (27 percent; $p<0.01$). There was no difference between groups in the percentage of patients with normalized MSLT (25 to 29 percent).

armodafinil (Nuvigil) versus placebo – OSAHS

The effectiveness of armodafinil in improving wakefulness in patients with excessive sleepiness associated with OSAHS was established in two 12-week studies of outpatients who met the International Classification of Sleep Disorders (ICSD) criteria for OSAHS (which are also consistent with the American Psychiatric Association DSM-IV criteria).[238] In addition, all patients had excessive sleepiness per the ESS, despite treatment with continuous positive airway pressure (CPAP). In the first study, a total of 395 patients with OSAHS were randomized to receive armodafinil 150 mg/day, armodafinil 250 mg/day, or matching placebo every day for 12 weeks. In the second study, 263 patients with OSAHS were randomized to either armodafinil 150 mg/day or placebo. In both studies, patients treated with armodafinil showed improved wakefulness and overall clinical condition.

A 12-week, randomized, double-blind study evaluated armodafinil 150 mg/day compared to placebo as an adjunct treatment for residual excessive sleepiness in 259 patients with OSAHS who were otherwise well controlled with nCPAP.[239] The authors assessed the ability of armodafinil to improve wakefulness and cognition and reduce fatigue in this population. Efficacy assessments were done at baseline and weeks four, eight, and 12. At the final visit, mean Maintenance of Wakefulness Test (MWT) sleep latency increased from baseline with armodafinil and decreased in the placebo group ($p=0.0003$). Armodafinil improved Clinical Global Impression of Change compared to placebo ($p=0.0069$). Armodafinil significantly improved episodic secondary memory ($p=0.0102$) and patient-estimated wakefulness ($p<0.01$) and reduced fatigue ($p<0.05$) compared with placebo. Armodafinil did not adversely affect nCPAP use. The most common adverse event associated with armodafinil was headache.

armodafinil (Nuvigil) versus placebo – narcolepsy

Patients with excessive sleepiness, as documented by a mean sleep latency test (MSLT) with a sleep latency of six minutes or less and the absence of any other clinically significant active medical or psychiatric disorder, were enrolled in a 12-week study of outpatients who met the ICSD criteria for narcolepsy.[240] A total of 196 patients were randomized to receive armodafinil 150 or 250 mg/day or matching placebo. Patients treated with armodafinil showed improved wakefulness and overall clinical condition.

armodafinil (Nuvigil) versus placebo – SWSD

The effectiveness of armodafinil in patients with excessive sleepiness associated with SWSD was demonstrated in a 12-week double-blind, placebo-controlled, parallel-group clinical trial. A total of 254 patients with chronic SWSD of moderate or greater severity were randomized to receive armodafinil 150 mg/day or placebo.[241,242] Patients treated with armodafinil showed a statistically significant prolongation in the time to sleep onset, as measured by the nighttime MSLT at final visit (armodafinil MSLT at baseline=2.3, week 12=5.3; placebo at baseline=2.4, week 12=2.8; $p<0.001$), and improvement in overall clinical condition ratings were seen for armodafinil (79 percent) compared to placebo-treated patients (59 percent; $p=0.001$).

META-ANALYSES

Several meta-analyses and reviews support the short-term efficacy of stimulant medications in reducing the core symptoms of ADHD - inattention, hyperactivity and impulsivity.[243,244,245,246,247] Research to date has not shown clear advantages of one stimulant medication over another or between dosage forms of a given agent. In the policy statement, AAP states that stimulants are equally effective for ADHD. Many children who fail to respond to one medication will have a positive response to an alternative stimulant.[248]

A meta-analysis of 29 randomized, double-blind, placebo-controlled studies involving over 4,465 children (mean age 10 years) with ADHD showed that MPH and MAS are significantly more effective than non-stimulant medications used to treat ADHD (atomoxetine, bupropion, desipramine, and modafinil).[249] Among stimulants, the meta-analysis found no difference in efficacy among MAS and MPH or among immediate-release or extended-release agents. The manufacturer of mixed amphetamine salts ER (Adderall XR) and MPH transdermal patch (Daytrana) funded this meta-analysis.

SUMMARY

The 2011 American Academy of Pediatrics Clinical Practice Guideline for the School Aged Child with ADHD recommends stimulant medication and/or behavioral therapy for the treatment of ADHD in children. The guidelines state that in many cases the stimulants improve the child's ability to follow rules and decrease emotional overactivity, leading to improved relationships.

Due to potential difficulties created by multiple daily dosing (e.g., compliance, social stigma, availability and willingness of schools and school staff to store and administer medication, potential for drug diversion), once-daily dosage forms may, in some situations, be preferred.

Several medications have been shown to be effective in treating ADHD. Except for atomoxetine (Strattera), clonidine ER (Kapvay), and guanfacine ER (Intuniv), all of the drugs approved for treatment of ADHD by the FDA are stimulants and are classified as controlled substances. The individual agents used for the treatment of ADHD are associated with different contraindications and precautions for use; this may influence the selection of appropriate therapy in patients with comorbidities (e.g., coexistent tic disorders or Tourette's syndrome).

For school-age children, the once daily dosage forms of MPH enhance compliance and decrease the risk of diversion. Quillivant XR, an extended-release MPH suspension, is an option for those patients who cannot swallow tablets or capsules and have failed treatment with other long-acting products that can be opened over applesauce. Mixed amphetamine salts (Adderall, Adderall XR) provide an alternative for patients who can not tolerate MPH. Clinical trials of dextroamphetamine (Dexedrine, Zenzedi, Procentra) are generally of poor quality and are somewhat dated. Additionally, dextroamphetamine has a greater potential for diversion and misuse than the other drugs used for ADHD. As a result, the dextroamphetamine formulations would not be the best initial choice over MPH to be used as first-line therapy for the majority of children and adolescents with ADHD.

Lisdexamfetamine dimesylate (Vyvanse), a prodrug of dextroamphetamine, was designed to have an extended duration of effect to allow for once daily dosing and to have less potential for abuse, diversion, or overdose toxicity. However, there is no evidence that it offers an advantage over any other formulation of amphetamine for treatment of children with ADHD.

Atomoxetine, clonidine ER, and guanfacine ER are non-stimulants that should not be addictive and are not scheduled drugs. However, atomoxetine has some of the same adverse effects as the stimulants, including increased heart rate, blood pressure, and potential growth retardation. Children treated with atomoxetine have also exhibited modest decreases in weight from baseline. Atomoxetine may be a useful agent in patients with a comorbid diagnosis such as anxiety and tic disorders. Clonidine ER and guanfacine ER also have cardiac adverse events as well as sedative properties. None of these products have shown increased effectiveness relative to other drugs in this class in comparative trials.

Modafinil (Provigil) and armodafanil (Nuvigil) may provide a slightly different profile of adverse effects than the stimulant medications traditionally used for the treatment of narcolepsy.

REFERENCES

1 Nuvigil [package insert]. Frazer, PA; Cephalon; June 2013.
2 Focalin [package insert]. East Hanover, NJ; Novartis; December 2013.
3 Zenzedi [package insert]. Atlanta, GA; Arbor Pharmaceuticals; January 2014.
4 Procentra [package insert]. Charlotte, NC; FSC Laboratories; June 2010.
5 Desoxyn [package insert]. Deerfield, IL; Ovation Pharmaceuticals; December 2013.
6 Methylin [package insert]. St. Louis, MO, Mallinckrodt; December 2013.
7 Ritalin/Ritalin-SR [package insert]. East Hanover, NJ; Novartis; December 2013.
8 Adderall [package insert]. Pomona, NY; Barr Laboratories, Inc. June 2013.
9 Provigil [package insert]. West Chester, PA; Cephalon; December 2010.
10 Focalin XR [package insert]. East Hanover, NJ; Novartis; December 2013.
11 Dexedrine Spanule [package insert]. Horsham, PA; Amedra Pharmaceuticals; October 2013.
12 Vyvanse [package insert]. Wayne, PA: Shire Pharmaceuticals Inc; December 2013.
13 Ritalin/Ritalin-SR [package insert]. East Hanover, NJ; Novartis; December 2013.
14 Metadate ER [package insert]. Rochester, NY; Medeva Pharm; January 2014.
15 Concerta [package insert]. Titusville, NJ; McNeil Pediatrics, Division of OMJPI; December 2013.
16 Metadate CD [package insert]. Smyrna, GA; UCB, Inc.; December 2013.
17 Quillivant XR [package insert]. Cupertino, CA; NextWave Pharmaceuticals, Inc., December 2013.
18 Ritalin LA [package insert]. East Hanover, NJ; Novartis; December 2013.
19 Daytrana [package insert]. Wayne, PA; Shire Pharmaceuticals; October 2013.
20 Adderall XR [package insert]. Wayne, PA; Shire US; December 2013.
21 Strattera [package insert]. Indianapolis, IN; Eli Lilly; February 2014.
22 Kapvay [package insert]. Florham Park, NJ; Shionogi Pharma; February 2013.
23 Intuniv [package insert]. Wayne, PA; Shire Pharmaceuticals, Inc.; August 2013.
24 Greenhill LL, Pliszka S, Dulcan MK, et al. Practice parameter for the use of stimulant medications in the treatment of children, adolescents, and adults. J Am Acad Child Adolesc Psychiatry. 2002; 41:26S-49S.
25 American Academy of Pediatrics. Subcommittee on Attention-Deficit/Hyperactivity Disorder and Steering Committee on Quality Improvement and Management. ADHD: Clinical Practice Guideline for the Diagnosis, Evaluation, and Treatment of Attention-Deficit/Hyperactivity Disorder in Children and Adolescents. Pediatrics, 2011; 128(5):1007-1022.
26 Brown RT, Amler RW, Freeman WS, et al. Treatment of attention-deficit/hyperactivity disorder: overview of the evidence. Pediatrics. 2005; 115:e749-57.
27 Goldman LS, Genel M, Bezman RJ, et al. Diagnosis and treatment of attention-deficit/hyperactivity disorder in children and adolescents. JAMA. 1998; 279:1100-7.
28 Elia J, Ambrosini J, Rapoport JL. Treatment of attention -deficit hyperactivity disorder. N Engl J Med. 1999; 340:780-8.
29 National Institute of Health: National Institutes of Health consensus development conference statement: Diagnosis and treatment of attention-deficit/hyperactivity disorder (ADHD). J Am Acad Child Adolesc Psychiatry. 2000; 39:192-3.
30 Barkley RA. Attention Deficit Hyperactivity Disorder: A Handbook for Diagnosis and Treatment. 2nd ed. New York, NY: Guilford Press; 1996.
31 American Academy of Pediatrics. Subcommittee on Attention-Deficit/Hyperactivity Disorder and Steering Committee on Quality Improvement and Management. ADHD: Clinical Practice Guideline for the Diagnosis, Evaluation, and Treatment of Attention-Deficit/Hyperactivity Disorder in Children and Adolescents. Pediatrics, 2011; 128(5):1007-1022.
32 Kessler RC, Adler L, Barkley R, et al. The prevalence and correlated of adult ADHD in the United States; results from the National Comorbidity Survey Replication. Am J Psychiatry. 2006; 163:716-23.
33 Zentall SS. Research on the educational implications of Attention Deficit Hyperactivity Disorder. Exceptional Child. 1993; 60:143-53.
34 Almond BW, Tranner JL, Goffman HG: The Family is the Patient: Using Family Interviews in Children 's Medical Care, 2nd ed. Baltimore, MD: Williams & Wilkins, 1999, pp 307-13.
35 Biederman J, Faraone SV, Spencer T, et al. Patterns of psychiatric comorbidity, cognition, and psychosocial functioning in adults with Attention Deficit Hyperactivity Disorder. Am J Psychiatry. 1993; 150:1792-8.
36 Zentall SS. Research on the educational implications of attention deficit hyperactivity disorder. Exceptional Child. 1993; 60:143-53.

37 Schachar R, Taylor E, Weiselberg MB, et al. Changes in family functioning and relationships in children who respond to methylphenidate. J Am Acad Child Adolesc Psychiatry. 1987; 26:728-32.
38 American Academy of Pediatrics. Subcommittee on Attention-Deficit/Hyperactivity Disorder and Steering Committee on Quality Improvement and Management. ADHD: Clinical Practice Guideline for the Diagnosis, Evaluation, and Treatment of Attention-Deficit/Hyperactivity Disorder in Children and Adolescents. Pediatrics, 2011; 128(5):1007-1022. Available at: http://pediatrics.aappublications.org/content/early/2011/10/14/peds.2011-2654.full.pdf . Accessed May 16. 2014.
39 American Academy of Pediatrics. Subcommittee on Attention-Deficit/Hyperactivity Disorder and Steering Committee on Quality Improvement and Management. ADHD: Clinical Practice Guideline for the Diagnosis, Evaluation, and Treatment of Attention-Deficit/Hyperactivity Disorder in Children and Adolescents. Pediatrics, 2011; 128(5):1007-1022. Available at: http://pediatrics.aappublications.org/content/early/2011/10/14/peds.2011-2654.full.pdf. Accessed May 16, 2014.
40 American Academy of Pediatrics. Subcommittee on Attention-Deficit/Hyperactivity Disorder and Steering Committee on Quality Improvement and Management. ADHD: Clinical Practice Guideline for the Diagnosis, Evaluation, and Treatment of Attention-Deficit/Hyperactivity Disorder in Children and Adolescents. Pediatrics, 2011; 128(5):1007-1022. Available at: http://pediatrics.aappublications.org/content/early/2011/10/14/peds.2011-2654.full.pdf. Accessed May 16, 2014.
41 Rappley MD. Clinical practice. Attention deficit-hyperactivity disorder. N Engl J Med. 2005; 352:165-73.
42 Biederman J, Faraone SV, Spencer T, et al. Patterns of psychiatric comorbidity, cognition, and psychosocial functioning in adults with Attention Deficit Hyperactivity Disorder. Am J Psychiatry. 1993; 150:1792-8.
43 Biederman J, Faraone S, Milberger S, et al. Predictors of persistence and remissions of ADHD into adolescence: Results from a four-year prospective follow-up study. J Am Acad Child Adolesc Psychiatry. 1996; 35:343-51.
44 Barbaresi WJ, Katusic SK, Colligan RC, et al. Long-term stimulant medication treatment of attention-deficit/hyperactivity disorder: results from a population-based study. J Dev Behav Pediatr. 2006; 27:1-10.
45 American Academy of Pediatrics. Subcommittee on Attention-Deficit/Hyperactivity Disorder and Steering Committee on Quality Improvement and Management. ADHD: Clinical Practice Guideline for the Diagnosis, Evaluation, and Treatment of Attention-Deficit/Hyperactivity Disorder in Children and Adolescents. Pediatrics, 2011; 128(5):1007-1022. Available at: http://pediatrics.aappublications.org/content/early/2011/10/14/peds.2011-2654.full.pdf. Accessed May 16, 2014.
46 Drugs for Treatment of ADHD. Treatment Guidelines from The Medical Letter. 2011: 9:23-28.
47 Kingshott RN, Vennelle M, Hoy CJ, et al. Predictors of improvements in daytime function outcomes with CPAP therapy. Am J Respir Crit Care Med. 2000; 161:866-71.
48 Engleman HM, Martin SE, Deary IJ, et al. Effect of continuous positive airway pressure treatment on daytime function in sleep apnea/hypopnoea syndrome. Lancet. 1994; 343:572-5.
49 Kribbs NB, Pack AI, Kline LR, et al. Effects of one night without nasal CPAP treatment on sleep and sleepiness in patients with obstructive sleep apnea. Am Rev Respir Dis. 1993; 147:1162-8.
50 Bedard M-A, Montplaisir J, Malo J, et al. Persistent neuropsychological deficits and vigilance impairment in sleep apnea syndrome after treatment with continuous positive airways pressure (CPAP). J Clin Exp Neuropsychol. 1993; 15:330-41.
51 Sforza E, Krieger J. Daytime sleepiness after long-term continuous positive airway pressure (CPAP) treatment in obstructive sleep apnea syndrome. J Neurol Sci. 1992; 110:21–6.
52 Stradling JR, Davies RJO. Is more NCPAP better? Sleep. 2000; 23:Suppl 4:S150-S153.
53 Gilman AG, Goodman LS, Rall TW, et al. The pharmacologic basis of therapeutics. New York: Macmillan; 1985.
54 U.S. Modafinil in Narcolepsy Multicenter Study Group. Randomized trial of modafinil as a treatment for the excessive daytime somnolence of narcolepsy. Neurology. 2000; 54:1166-75.
55 Nuvigil [package insert]. Frazer, PA; Cephalon; June 2013.
56 Desoxyn [package insert]. Deerfield, IL; Ovation Pharmaceuticals; December 2013.
57 Shenker A. The mechanism of action of drugs used to treat attention-deficit hyperactivity disorder: focus on catecholamine receptor pharmacology. Adv Pediatr. 1992; 39:337-82.
58 Srinivas NR, Hubbard JW, Quinn D, et al. Enantioselective pharmacokinetics and pharmacodynamics of dl-threo-methylphenidate in children with attention deficit hyperactivity disorder. Clin Pharmacol Ther. 1992; 52:561-8.
59 Patrick KS, Caldwell RW, Ferris RM, et al. Pharmacology of the enantiomers of threo-methylphenidate. J Pharmacol Exp Ther. 1987; 241:152-8.
60 The Medical Letter. 2007; 49(1265):58-9.
61 Vyvanse [package insert]. Wayne PA: Shire Pharmaceuticals Inc; December2013.
62 Pelham WE Jr, Greenslade KE, Vodde-Hamilton M, et al. Relative efficacy of long-acting stimulants on children with attention deficit-hyperactivity disorder: a comparison of standard methylphenidate, sustained-release methylphenidate, sustained-release dextroamphetamine, and pemoline. Pediatrics. 1990; 86:226-37.
63 Swanson J, Gupta S, Guinta D, et al. Acute tolerance to methylphenidate in the treatment of Attention Deficit Hyperactivity Disorder in children. Clin Pharmacol Ther. 1999; 66:295–305.
64 Brown RT, Amler RW, Freeman WS, et al. Treatment of attention-deficit/hyperactivity disorder: overview of the evidence. Pediatrics. 2005; 115:e749-57.
65 Bymaster FP, Katner JS, Nelson DL, et al. Atomoxetine increases extracellular levels of noradrenaline and dopamine in the prefrontal cortex of rat: a potential mechanism for efficacy in attention deficit/hyperactivity disorder. Neuropsychopharmacology. 2002; 27:699-711.
66 Michelson D, Faries D, Wernicke J, et al. Atomoxetine in the treatment of children and adolescents with attention-deficit/hyperactivity disorder: a randomised, placebo-controlled, dose-response study. Pediatrics. 2001;108:1-9.
67 Brown RT, Amler RW, Freeman WS, et al. Treatment of attention-deficit/hyperactivity disorder: overview of the evidence. Pediatrics. 2005; 115:e749-57.
68 Intuniv [package insert]. Wayne, PA; Shire Pharmaceuticals, Inc.; August 2013.
69 Kapvay [package insert]. Florham Park, NJ; Shionogi Pharma; February 2013.
70 Nuvigil [package insert]. Frazer, PA; Cephalon; June 2013.

71 Focalin [package insert]. East Hanover, NJ; Novartis; December 2013.
72 Dexedrine Spanule [package insert]. Horsham, PA; Amedra Pharmaceuticals; October 2013.
73 Zenzedi [package insert]. Atlanta, GA; Arbor Pharmaceuticals; January 2014.
74 Procentra [package insert]. Charlotte, NC; FSC Laboratories; June 2010.
75 Desoxyn [package insert]. Deerfield, IL; Ovation Pharmaceuticals; December 2013.
76 Ritalin/Ritalin-SR [package insert]. East Hanover, NJ; Novartis; December 2013.
77 Swanson JM, Kinsbourne M, Roberts W, et al. Time-response analysis of the effect of stimulant medication on the learning ability of children referred for hyperactivity. Pediatrics. 1978; 61:21-9.
78 Adderall [package insert]. Pomona, NY; Barr Laboratories, Inc. June 2013.
79 Provigil [package insert]. West Chester, PA; Cephalon; December 2010.
80 Focalin XR [package insert]. East Hanover, NJ; Novartis; December 2013.
81 Dexedrine Spanule [package insert]. Horsham, PA; Amedra Pharmaceuticals; October 2013.
82 The Medical Letter. 2007; 49(1265):58-9.
83 Vyvanse [package insert]. Wayne, PA: Shire Pharmaceuticals Inc; December 2013.
84 Biederman J, Krishnan S, Zhang Y, et al. Efficacy and tolerability of lisdexamfetamine dimesylate (NRP-104) in children with attention-deficit/hyperactivity disorder: a phase III, multicenter, randomized, double-blind, forced-dose, parallel-group study. Clin Ther. 2007; 29(3):450-63.
85 Ritalin/Ritalin-SR [package insert]. East Hanover, NJ; Novartis; December 2013.
86 Patrick KS, Straughn AB, Jarvi EJ, et al. The absorption of sustained-release methylphenidate formulations compared to an immediate-release formulation. Biopharm Drug Dispos. 1989; 10:165–71.
87 Birmaher B, Greenhill LL, Cooper TB, et al. Sustained release methylphenidate: Pharmacokinetic studies in ADHD males. J Am Acad Child Adolesc Psychiatry. 1989; 28:768–72.
88 Concerta [package insert]. Titusville, NJ; McNeil Pediatrics, Division of OMJPI; December 2013.
89 Swanson JM, Wigal SB, Wigal T, et al. A comparison of once-daily extended-release methylphenidate formulations in children with attention-deficit/hyperactivity disorder in the laboratory school (the Comacs Study). Pediatrics. 2004; 113:e206-16.
90 Metadate CD [package insert]. Smyrna, GA; UCB, Inc.; December 2013.
91 Quillivant XR [package insert]. Cupertino, CA; NextWave Pharmaceuticals, Inc., December 2013.
92 Ritalin LA [package insert]. East Hanover, NJ; Novartis; December 2013.
93 Daytrana [package insert]. Wayne, PA; Shire Pharmaceuticals; October 2013.
94 Adderall XR [package insert]. Wayne, PA; Shire US; December 2013.
95 Strattera [package insert]. Indianapolis, IN; Eli Lilly; February 2014.
96 Kapvay [package insert]. Florham Park, NJ; Shionogi Pharma; February 2013.
97 Intuniv [package insert]. Wayne, PA; Shire Pharmaceuticals, Inc.; August 2013.
98 Belle DJ, Ernest CS, Sauer JM, et al. Effect of potent CYP2D6 inhibition by paroxetine on atomoxetine pharmacokinetics. J Clin Pharmacol. 2002; 42:1219-27.
99 Sauer JM, Ponsler GD, Mattiuz EL, et al. Disposition and metabolic fate of atomoxetine hydrochloride: the role of CYP2D6 in human disposition and metabolism. Drug Metab Dispos. 2003; 31:98-107.
100 Corman SL, Fedutes BA, Culley CM. Atomoxetine: the first nonstimulant for the management of attention-deficit/hyperactivity disorder. Am J Health Syst Pharm. 2004; 61:2391-9.
101 Brown RT, Amler RW, Freeman WS, et al. Treatment of attention-deficit/hyperactivity disorder: overview of the evidence. Pediatrics. 2005; 115:e749-57.
102 Michelson D, Allen A, Busner J, et al. Once daily atomoxetine treatment for children and adolescents with attention deficit hyperactivity disorder: a randomised, placebo controlled study. Am J Psychiatry. 2002; 159:1896-901.
103 Intuniv [package insert]. Wayne, PA; Shire Pharmaceuticals, Inc.; August 2013.
104 Dexedrine Spanule [package insert]. Horsham, PA; Amedra Pharmaceuticals; October 2013.
105 Desoxyn [package insert]. Deerfield, IL; Ovation Pharmaceuticals; December 2013.
106 Vyvanse [package insert]. Wayne, PA: Shire Pharmaceuticals Inc; December 2013.
107 Adderall [package insert]. Pomona, NY; Barr Laboratories, Inc. June 2013.
108 Adderall XR [package insert]. Wayne, PA; Shire US; December 2013.
109 Ritalin/Ritalin-SR [package insert]. East Hanover, NJ; Novartis; December 2013.
110 Concerta [package insert]. Titusville, NJ; McNeil Pediatrics, Division of OMJPI; December 2013.
111 Ritalin LA [package insert]. East Hanover, NJ; Novartis; December 2013.
112 Daytrana [package insert]. Wayne, PA; Shire Pharmaceuticals; October 2013.
113 Focalin [package insert]. East Hanover, NJ; Novartis; December 2013.
114 Focalin XR [package insert]. East Hanover, NJ; Novartis; December 2013.
115 Strattera [package insert]. Indianapolis, IN; Eli Lilly; February 2014.
116 Provigil [package insert]. West Chester, PA; Cephalon; December 2010.
117 Intuniv [package insert]. Wayne, PA; Shire Pharmaceuticals, Inc.; August 2013.
118 Kapvay [package insert]. Florham Park, NJ; Shionogi Pharma; February 2013.
119 Quillivant XR [package insert]. Cupertino, CA; NextWave Pharmaceuticals, Inc., December 2013.
120 Lim JR, Faught PR, Chalasani NP, et al. Severe liver injury after initiating therapy with atomoxetine in two children. J Pediatr. 2006; 148:831-4.
121 FDA Drug Safety Communication: Safety Review Update of Medications used to treat Attention-Deficit/Hyperactivity Disorder (ADHD) in children and young adults. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm277770.htm. Last Updated December 20, 2011. Accessed May 16, 2014.
122 FDA Drug Safety Communication: Safety Review Update of Medications used to treat Attention-Deficit/Hyperactivity Disorder (ADHD) in adults. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm279858.htm. Last Updated December 15, 2011. Accessed May 16, 2014.
123 Ritalin/Ritalin-SR [package insert]. East Hanover, NJ; Novartis; December 2013.

124 Focalin [package insert]. East Hanover, NJ: Novartis; December 2013.
125 Keating GM, Figgitt DP. Dexmethylphenidate. Drugs. 2002; 62:1899-904.
126 Thiel A, Dressler D. Dyskinesias possibly induced by norpseudoephedrine. J Neurol. 1994; 24:167-9.
127 Dexedrine Spanule [package insert]. Horsham, PA; Amedra Pharmaceuticals; October 2013.
128 Strattera [package insert]. Indianapolis, IN; Eli Lilly; February 2014.
129 Hoffman BB, Lefkowitz RJ. Catecholamines and sympathomimetic drugs. Gilman AG, Rall TW, Nies AS, Taylor P, (eds.) In: Goodman and Gilman's Pharmacological Basis of Therapeutics. 8th ed., New York, Pergamon Press. 1990: 211-12.
130 Gibb JW, Bush L, Hanson GR. Exacerbation of methamphetamine-induced neurochemical deficits by melatonin. J Pharmacol Exp Ther. 1997; 283:630-5.
131 Angrist B, Gershon S. Variable attenuation of amphetamine effects by lithium. Am J Psychiatry. 1979; 136:806-10.
132 Dexedrine Spanule [package insert]. Horsham, PA; Amedra Pharmaceuticals; October 2013.
133 Eskalith [package insert]. Research Triangle Park, NC: GlaxoSmithKline; September 2003.
134 Koehler-Troy C, Strober M, Malenbaum R. Methylphenidate-induced mania in a prepubertal child. J Clin Psychiatry. 1986; 47:566-7.
135 Strattera [package insert]. Indianapolis, IN; Eli Lilly; February 2014.
136 Dexedrine Spanule [package insert]. Horsham, PA; Amedra Pharmaceuticals; October 2013.
137 Ritalin/Ritalin-SR [package insert]. East Hanover, NJ; Novartis; December 2013.
138 Focalin [package insert]. East Hanover, NJ: Novartis; December 2013.
139 Intuniv [package insert]. Wayne, PA; Shire Pharmaceuticals, Inc.; August 2013.
140 Intuniv [package insert]. Wayne, PA; Shire Pharmaceuticals, Inc.; August 2013.
141 Intuniv [package insert]. Wayne, PA; Shire Pharmaceuticals, Inc.; August 2013.
142 Kapvay [package insert]. Florham Park, NJ; Shionogi Pharma; February 2013.
143 Wong YN, Wang L, Hartman L, et al. Comparison of the single-dose pharmacokinetics and tolerability of modafinil and dextroamphetamine administered alone or in combination in healthy male volunteers. J Clin Pharmacol. 1998; 38:971-8.
144 Provigil [package insert]. West Chester, PA; Cephalon; December 2010.
145 Provigil [package insert]. West Chester, PA; Cephalon; December 2010.
146 Weiss G, Hechtman LT. Medication treatment of ADHD. In: Weiss G, Hechtman LT, eds. Hyperactive Children Grown Up. 2nd ed. New York, NY:Guilford Press;1993: 348-65.
147 Barkley RA, DuPaul GJ, Costello A. In: Werry JS, Aman MG, eds. Practitioner's Guide to Psychoactive Drugs for Children and Adolescents. New York, NY: Plenum Publishing Corporation; 1993: 205-37.
148 Elia J, Borcherding BG, Rapoport JL, et al. Methylphenidate and dextroamphetamine treatments of hyperactivity: are there true nonresponders? Psychiatry Res. 1991; 36:141-55.
149 Rapoport JL, Buchsbaum MS, Zahn TP, et al. Dextroamphetamine: cognitive and behavioral effects in normal prepubertal boys. Science. 1978; 199:560-3.
150 Efron D, Jarman F, Barker M. Side Effects of Methylphenidate and Dexamphetamine in Children With Attention-Deficit Hyperactivity Disorder: A Double-blind, Crossover Trial. Pediatrics. 1997; 100:662-6.
151 American Academy of Pediatrics. Subcommittee on Attention-Deficit/Hyperactivity Disorder and Committee on Quality Improvement. Clinical practice guideline: treatment of the school-aged child with attention-deficit/hyperactivity disorder. Pediatrics. 2001; 108:1033-44.
152 Nuvigil [package insert]. Frazer, PA; Cephalon; June 2013.
153 Focalin [package insert]. East Hanover, NJ; Novartis; December 2013.
154 Zenzedi [package insert]. Atlanta, GA; Arbor Pharmaceuticals; January 2014.
155 Procentra [package insert]. Charlotte, NC; FSC Laboratories; June 2010.
156 Desoxyn [package insert]. Deerfield, IL; Ovation Pharmaceuticals; December 2013.
157 Methylin [package insert]. St. Louis, MO, Mallinckrodt; December 2013.
158 Adderall [package insert]. Pomona, NY; Barr Laboratories, Inc. June 2013.
159 Provigil [package insert]. West Chester, PA; Cephalon; December 2010.
160 Focalin XR [package insert]. East Hanover, NJ; Novartis; December 2013.
161 Dexedrine Spanule [package insert]. Horsham, PA; Amedra Pharmaceuticals; October 2013.
162 Vyvanse [package insert]. Wayne PA: Shire Pharmaceuticals Inc; December 2013.
163 Ritalin/Ritalin-SR [package insert]. East Hanover, NJ; Novartis; December 2013.
164 Quillivant XR [package insert]. Cupertino, CA; NextWave Pharmaceuticals, Inc., December 2013.
165 Concerta [package insert]. Titusville, NJ; McNeil Pediatrics, Division of OMJPI; December2013.
166 Metadate CD [package insert]. Smyrna, GA; UCB, Inc.; December 2013.
167 Ritalin LA [package insert]. East Hanover, NJ; Novartis; December 2013.
168 Daytrana [package insert]. Wayne, PA; Shire Pharmaceuticals; October 2013.
169 Adderall XR [package insert]. Wayne, PA; Shire US; December 2013.
170 Strattera [package insert]. Indianapolis, IN; Eli Lilly; February 2014.
171 Kapvay [package insert]. Florham Park, NJ; Shionogi Pharma; February 2013.
172 Intuniv [package insert]. Wayne, PA; Shire Pharmaceuticals, Inc.; August 2013.
173 Brown RT, Amler RW, Freeman WS, et al. Treatment of attention-deficit/hyperactivity disorder: overview of the evidence. Pediatrics. 2005; 115:e749-57.
174 American Academy of Pediatrics. Subcommittee on Attention-Deficit/Hyperactivity Disorder and Steering Committee on Quality Improvement and Management. ADHD: Clinical Practice Guideline for the Diagnosis, Evaluation, and Treatment of Attention-Deficit/Hyperactivity Disorder in Children and Adolescents. Pediatrics, 2011; 128(5):1007-1022. Available at: http://pediatrics.aappublications.org/content/early/2011/10/14/peds.2011-2654.full.pdf. Accessed May 16, 2014.

175 Kratchovil CJ, Wilens TE, Greenhill LL, et al. Effects of long-term atomoxetine treatment for young children with attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry. 2006; 45:919-27.
176 Desoxyn [package insert]. Deerfield, IL; Ovation Pharmaceuticals; December 2013.
177 Vyvanse [package insert]. Wayne, PA: Shire Pharmaceuticals Inc; December2013.
178 Adderall [package insert]. Pomona, NY; Barr Laboratories, Inc. June 2013.
179 Adderall XR [package insert]. Wayne, PA; Shire US; December 2013.
180 Ritalin/Ritalin-SR [package insert]. East Hanover, NJ; Novartis; December 2013.
181 Concerta [package insert]. Titusville, NJ; McNeil Pediatrics, Division of OMJPI; December 2013.
182 Ritalin LA [package insert]. East Hanover, NJ; Novartis; December 2013.
183 Daytrana [package insert]. Wayne, PA; Shire Pharmaceuticals; October 2013.
184 Focalin [package insert]. East Hanover, NJ; Novartis; December 2013.
185 Focalin XR [package insert]. East Hanover, NJ; Novartis; December 2013.
186 Provigil [package insert]. West Chester, PA; Cephalon; December 2010.
187 Strattera [package insert]. Indianapolis, IN; Eli Lilly; February 2014.
188 Intuniv [package insert]. Wayne, PA; Shire Pharmaceuticals, Inc.; August 2013.
189 Kapvay [package insert]. Florham Park, NJ; Shionogi Pharma; February 2013.
190 Quillivant XR [package insert]. Cupertino, CA; NextWave Pharmaceuticals, Inc., December 2013.
191 Greenhill LL, Pliszka S, Dulcan MK, et al. Practice parameter for the use of stimulant medications in the treatment of children, adolescents, and adults. J Am Acad Child Adolesc Psychiatry. 2002; 41:26S-49S.
192 Zito J. Trends in the prescribing of psychotropic medications to preschoolers. JAMA. 2000; 283:1025-30.
193 Ruff ME. Attention Deficit Disorder and Stimulant Use: An Epidemic of Modernity. Clin Pediatr. 2005; 44:557-63.
194 Nuvigil [package insert]. Frazer, PA; Cephalon; June 2013.
195 Focalin [package insert]. East Hanover, NJ; Novartis; December 2013.
196 Zenzedi [package insert]. Atlanta, GA; Arbor Pharmaceuticals; January 2014.
197 Procentra [package insert]. Charlotte, NC; FSC Laboratories; June 2010.
198 Desoxyn [package insert]. Deerfield, IL; Ovation Pharmaceuticals; December 2013.
199 Methylin [package insert]. St. Louis, MO, Mallinckrodt; December 2013.
200 Adderall [package insert]. Pomona, NY; Barr Laboratories, Inc. June 2013.
201 Provigil [package insert]. West Chester, PA; Cephalon; December 2010.
202 Focalin XR [package insert]. East Hanover, NJ; Novartis; December 2013.
203 Dexedrine Spanule [package insert]. Horsham, PA; Amedra Pharmaceuticals; October 2013.
204Vyvanse [package insert]. Wayne PA: Shire Pharmaceuticals Inc; December2013.
205 Ritalin/Ritalin-SR [package insert]. East Hanover, NJ; Novartis; December 2013.
206 Concerta [package insert]. Titusville, NJ; McNeil Pediatrics, Division of OMJPI; December2013.
207 Metadate CD [package insert]. Smyrna, GA; UCB, Inc.; December 2013.
208 Quillivant XR [package insert]. Cupertino, CA; NextWave Pharmaceuticals, Inc., December 2013.
209 Ritalin LA [package insert]. East Hanover, NJ; Novartis; December 2013.
210 Daytrana [package insert]. Wayne, PA; Shire Pharmaceuticals; October 2013.
211 Adderall XR [package insert]. Wayne, PA; Shire US; December 2013.
212 Strattera [package insert]. Indianapolis, IN; Eli Lilly; February 2014.
213 Kapvay [package insert]. Florham Park, NJ; Shionogi Pharma; February 2013.
214 Intuniv [package insert]. Wayne, PA; Shire Pharmaceuticals, Inc.; August 2013.
215 Nuvigil [package insert]. Frazer, PA; Cephalon; June 2013.
216 Spencer T, Heiligenstein JH, Biederman J, et al. Results from 2 proof-of-concept, placebo-controlled studies of atomoxetine in children with attention-deficit/hyperactivity disorder. J Clin Psychiatry. 2002; 63:1140-7.
217 Biederman J, Heiligenstein JH, Faries DE, et al. Efficacy of Atomoxetine Versus Placebo in School-Age Girls With Attention-Deficit/Hyperactivity Disorder. Pediatrics. 2002; 110:75-82.
218 Newcorn JH, Kratochvil CJ, Allen AJ, et al. Atomoxetine and osmotically released methylphenidate for the treatment of attention deficit hyperactivity disorder: acute comparison and differential response. Am J Psychiatry. 2008; 165(6):721-730.
219 Sangal RB, Owens J, Allen AJ, et al. Effects of atomoxetine and methylphenidate on sleep in children with ADHD. Sleep. 2006; 29(12):1573-85.
220 Kapvay [package insert]. Florham Park, NJ; Shionogi Pharma; February 2013.
221 Intuniv [package insert]. Wayne, PA; Shire Pharmaceuticals, Inc.; August 2013.
222 Wilson HK, Cox DJ, Merkel RL, et al. Effect of extended release stimulant-based medications on neuropsychological functioning among adolescents with Attention-Deficit/Hyperactivity Disorder. Arch Clin Neuropsychol. 2006; 21(8):797-807.
223 Wigal S, Swanson JM, Feifel D, et al. A double-blind, placebo-controlled trial of dexmethylphenidate hydrochloride and d,l-threo-methylphenidate hydrochloride in children with attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry. 2004; 43:1406-14.
224 Parasrampuria DA, Schoedel KA, Schuller R, et al. Assessment of pharmacokinetics and pharmacodynamic effects related to abuse potential of a unique oral osmotic-controlled extended-release methylphenidate formulation in humans. J Clin Pharmacol. 2007; 47(12):1476-88.
225 Wolraich ML, Greenhill LL, Pelham W, et al. Randomized, controlled trial of OROS methylphenidate once a day in children with attention-deficit/hyperactivity disorder. Pediatrics. 2001; 108:883-92.
226 Wigal SB, Childress AC, et al. NWP06, an Extended-Release Oral Suspension of Methylphenidate, Improved Attention-Deficit/Hyperactivity Disorder Symptoms Compared with Placebo in a Laboratory Classroom Study. J Child Adolesc Psychopharmacol. 2013; (1)3-10. Available at: http://online.liebertpub.com/doi/pdf/10.1089/cap.2012.0073. Accessed May 16, 2014.
227 Buckstein OG, et al. Parent and Teacher Rated Effects of MTS and OROS Methylphenidate in ADHD. Poster presented at the 159th Annual Meeting of the American Psychiatric Association Annual Meeting, Toronto, Canada; May 24, 2006.

228 Biederman J, Krishnan S, Zhang Y, et al. Efficacy and tolerability of lisdexamfetamine dimesylate (NRP-104) in children with attention-deficit/hyperactivity disorder: a phase III, multicenter, randomized, double-blind, forced-dose, parallel-group study. Clin Ther. 2007; 29(3):450-63.
229 Vyvanse [package insert]. Wayne, PA: Shire Pharmaceuticals Inc; December 2013.
230 Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep. 1991; 14:540-5.
231 Johns MW. Reliability and factor analysis of the Epworth sleepiness scale. Sleep. 1992; 15:376-81.
232 Mitler MM, Gujavarty KS, Browman CP. Maintenance of wakefulness test: a polysomnographic technique for evaluating treatment of patients with excessive somnolence. Electroencephalogr. Clin. Neurophysiol. 1982; 153:658-61.
233 Richardson GS, Carskadon MA, Flagg W, et al. Excessive daytime sleepiness in man: multiple sleep latency measurement in narcoleptic and control subjects. Electroencephalogr. Clin. Neurophysiol. 1978; 45:621-7.
234 Carskadon MA, Dement WC, Mitler MM, et al. Guidelines for the Multiple Sleep Latency Test (MSLT): a standard measure of sleepiness. Sleep. 1986; 9:519-24.
235 Johns M. Sensitivity and specificity of the multiple sleep latency test (MSLT), the maintenance of wakefulness test and the Epworth sleepiness scale: Failure of the MSLT as a gold standard. Journal of Sleep Research. 2000; 9:5-11.
236 US Modafinil in Narcolepsy Multicenter Study Group. Randomized trial of modafinil for the treatment of pathological somnolence in narcolepsy. Ann Neurol. 1998; 43:88-97.
237 Pack AI, Black JE, Schwartz JRL, et al. Modafinil as Adjunct Therapy for Daytime Sleepiness in Obstructive Sleep Apnea. Am J Respir Crit Care Med. 2001; 164:1675-81.
238 Nuvigil [package insert]. Frazer, PA; Cephalon; June 2013.
239 Hirschkowitz M, Black JE, et al. Adjunct armodafinil improves wakefulness and memory in obstructive sleep apnea/hypopnea syndrome. Respir Med. 2007; 101(3):616-27.
240 Nuvigil [package insert]. Frazer, PA; Cephalon; June 2013.
241 Nuvigil [package insert]. Frazer, PA; Cephalon; June 2013.
242 Czeisler CA, Walsh JK, Wesnes KA, et al. Armodafinil for treatment of excessive sleepiness associated with shift work disorder: a randomized controlled study. Mayo Clin Proc. 2009; 84(11):958-72.
243 Kavale K. The efficacy of stimulant drug treatment for hyperactivity: a meta-analysis. J Learn Disabil. 1982; 15:280-9.
244 Ottenbacher KJ. Drug treatment of hyperactivity in children. Dev Med Child Neurol. 1983; 25:358-66.
245 Thurber S. Medication and hyperactivity. A meta-analysis. J Gen Psychol. 1983; 108:79-86.
246 Swanson JM, McBurnett K, Wigal T, et al. Effect of stimulant medication on children with attention-deficit disorder: a review of reviews. Except Child. 1993; 60:154-62.
247 Faraone SV. Comparing the Efficacy of Medications for ADHD Using Meta-Analysis. Poster presented at the 159th Annual Meeting of the American Psychiatric Association, Toronto, Canada; May 24, 2006.
248 American Academy of Pediatrics. Subcommittee on Attention-Deficit/Hyperactivity Disorder and Steering Committee on Quality Improvement and Management. ADHD: Clinical Practice Guideline for the Diagnosis, Evaluation, and Treatment of Attention-Deficit/Hyperactivity Disorder in Children and Adolescents. Pediatrics, 2011; 128(5):1007-1022. Available at: http://pediatrics.aappublications.org/content/early/2011/10/14/peds.2011-2654.full.pdf. Accessed May 16, 2014.
249 Faraone SV. Comparing the Efficacy of Medications for ADHD Using Meta-Analysis. Poster presented at the 159th Annual Meeting of the American Psychiatric Association, Toronto, Canada; May 24, 2006.

